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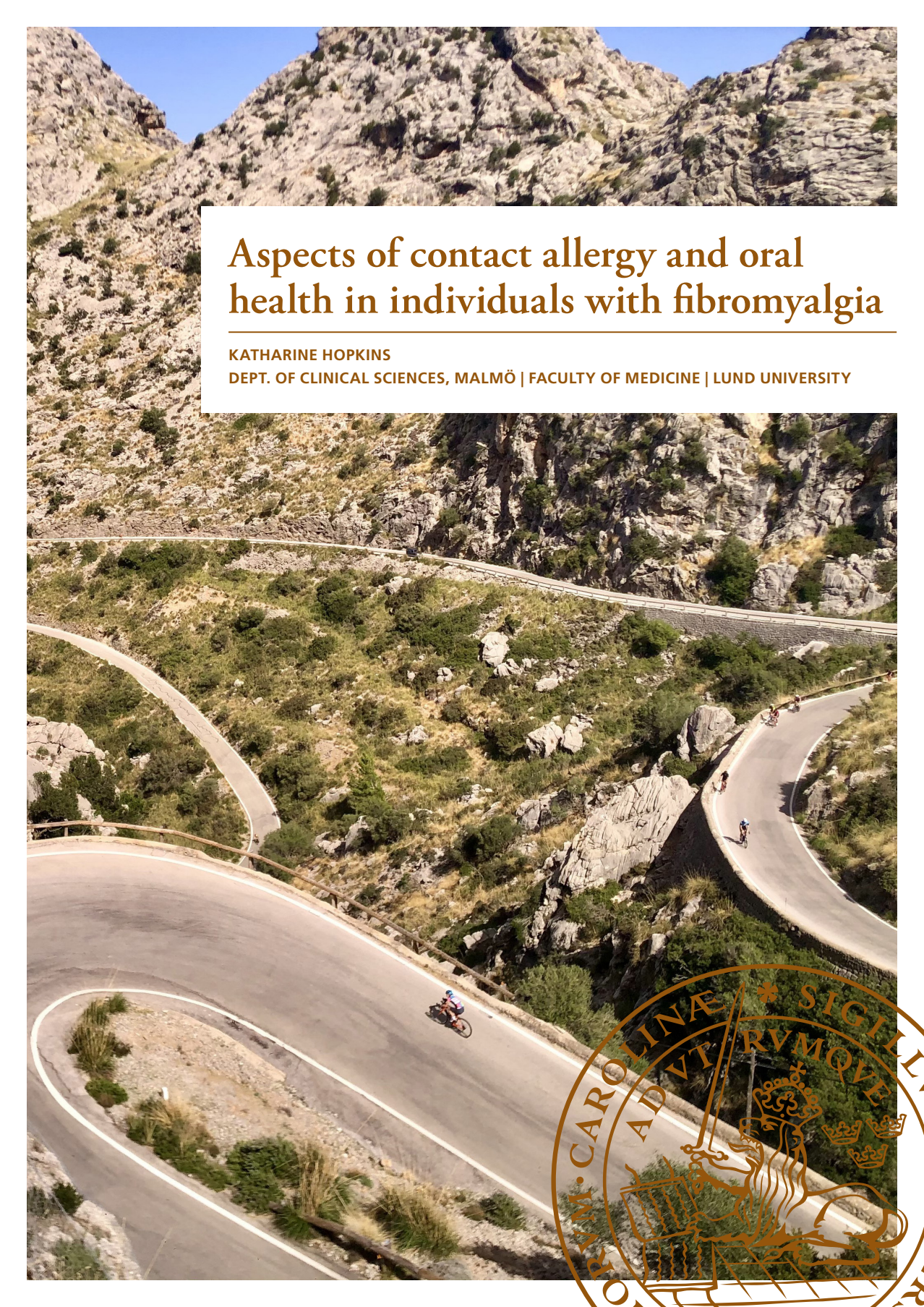
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Aspects of contact allergy and oral health in individuals with fibromyalgia

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DEPT. OF CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

Aspects of contact allergy and oral health in
individuals with fibromyalgia

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Katharine Hopkins



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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 11th of September 2026 at 01.00 p.m. in Kvinnoklinikens aula, Jan Waldenströms gata 47, Skåne University Hospital, Malmö.

Faculty opponent

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Abstract:

The aim of this thesis was to assess whether contact allergy could be significant in chronic pain syndromes, using fibromyalgia (FM) as a model. Given our knowledge of the role of gold allergy in systemic contact dermatitis, a specific focus on gold allergy would form part of the project. Specific aims included assessing the prevalence and pattern of contact allergy in individuals with FM, assessing the clinical relevance of gold allergy in FM, and examining the oral status of individuals with FM.

Prevalence of contact allergy in FM was assessed with patch testing and comparing with control groups. Questionnaires were used to assess relevance of positive patch test reactions and quality of life in FM. A dental examination was used to assess the oral health of individuals with FM and compare with a population control group.

119 females with FM were recruited to the patch test studies. The FM group had an overrepresentation of contact allergy to nickel ($p = 0.0004$), *Myroxylon pereirae* ($p = 0.00004$) and Fragrance mix I ($p = 0.010$) compared with population controls. There were significantly more reactions to the Swedish baseline series in the FM group ($p < 0.0001$) than in population controls. Testing with an extended dental series showed a significantly higher prevalence of gold allergy in individuals with FM than in dermatitis controls ($p = 0.043$) and significantly more positive reactions for (meth)acrylates than a control group with oral symptoms ($p = 0.016$). Significantly more participants with gold allergy reported cutaneous symptoms upon contact with gold compared with those who did not have gold allergy ($p = 0.010$). Gold contact allergy was also overrepresented in those with oral symptoms ($p = 0.024$). Visual analogue scores showed that those with oral symptoms and gold allergy scored significantly higher in the domains of pain, tiredness, and malaise. FM individuals had a higher stage of periodontal disease than controls ($p = 0.017$) and a higher frequency of oral lesions ($p < 0.001$). The FM group reported poor oral health related quality of life scores.

The contact allergies overrepresented in FM include those where sensitisation may occur via the oral mucosa. Gold in particular is described in systemic contact dermatitis. Periodontal disease is associated with systemic inflammation. Contact allergy may play a role in poorer oral health and systemic inflammation in FM.

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'I thought of that while riding my bicycle'
Albert Einstein

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List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals. The articles are appended at the end of the thesis.

Paper I

Bruze M, Hopkins K, Dahlin J, Olsson K, Åstrand J, Svedman C, Ofenloch R, Antelmi A. **Increased rates of fragrance allergy in fibromyalgia individuals tested with the Swedish baseline patch test series.** J Eur Acad Dermatol Venereol. 2023 Jan;37(1):104-113. doi: 10.1111/jdv.18562. Epub 2022 Sep 7. PMID: 36018078.

Paper II

Hopkins K, Antelmi A, Dahlin J, Olsson K, Svedman C, Åstrand J, Bruze M. **Increased Rates of Gold and Acrylate Allergy in Individuals with Fibromyalgia Tested with an Extended Dental Patch Test Series.** Acta Derm Venereol. 2023 Dec 11;103:adv22336. doi: 10.2340/actadv.v103.22336. PMID: 38078690; PMCID: PMC10726376.

Paper III

Hopkins K, Antelmi A, Dahlin J, Olsson K, Svedman C, Åstrand J, Olsson P, Bruze M. **Clinical Relevance of Contact Allergy to Gold Sodium Thiosulphate in Fibromyalgia.** Acta Derm Venereol. 2025 Mar 27;105:adv42463. doi: 10.2340/actadv.v105.42463. PMID: 40150947; PMCID: PMC11971835.

Paper IV

Hopkins K, Ahlgren C, Wahlin Å, Antelmi A, Bruze M, Svedman C. **Increased risk of periodontal disease and poor oral related quality of life in fibromyalgia** (submitted)

Statement on the use of artificial intelligence

No generative artificial intelligence (AI) tools were used in the production of this thesis.

Thesis at a glance

Study and objective	Method	Main findings/conclusion
I. To assess the prevalence and pattern of contact allergy to the Swedish baseline series in individuals with fibromyalgia (FM), and compare with control groups.	Cross-sectional study. Patch testing of individuals with FM with the Swedish baseline series and comparing with dermatitis controls tested at the Department of Occupational and Environmental Dermatology (DOED), Malmö, and general population controls drawn from a study assessing prevalence of contact allergy in the general population.	Contact allergy to nickel, <i>Myroxylon pereirae</i> and fragrance mix I were significantly overrepresented in the FM group compared with population controls. Significantly more reactions to allergens in the Swedish baseline series in the FM group than in population controls.
II. To assess the prevalence and pattern of contact allergy to an extended dental series in individuals with FM, and compare with control groups.	Cross-sectional study. Patch testing of individuals with FM with an extended dental series and comparing with dermatitis controls and patients with oral symptoms tested at the DOED.	Significantly higher prevalence of gold allergy in individuals with FM than in dermatitis controls. Significantly more positive reactions for (meth)acrylates than the control group with oral symptoms.
III. To assess the clinical relevance of contact allergy to gold in individuals with FM.	Cross-sectional questionnaire study. Participants with FM who participated in studies I and II. Questions regarding exposure to gold and cutaneous and oral symptoms related to gold exposure. Rating of FM symptoms using a visual analogue scale (VAS).	Cutaneous symptoms upon contact with gold were significantly overrepresented in those with gold allergy. Gold contact allergy was overrepresented in those with oral symptoms. VAS scores in all domains significantly higher in those with oral symptoms and gold allergy.
IV. i) To assess the oral health and oral quality of life of individuals with FM, and compare with population controls. ii) To assess the clinical relevance of contact allergy with respect to oral findings in individuals with FM.	Cross-sectional study. Recruitment of individuals with FM from participants in studies I-III. Questionnaire on aspects of oral health, oral hygiene habits and oral related quality of life measurements using the Oral Health Impact Profile (OHIP-14). Dental examination including assessment of periodontal disease. Controls drawn from a population study assessing oral health in the general population. Assessment of contact allergy in the FM group, related to oral examination findings and symptoms.	FM individuals had a higher stage of periodontal disease and a significantly higher frequency of oral lesions than controls. The FM group reported high OHIP-14 scores, indicating poor oral-related quality of life. No relationship was observed between contact allergy and oral symptoms or clinical findings in the FM group.

Abbreviations

ACD	Allergic contact dermatitis
DC	Dendritic cells
DOED	Department of Occupational and Environmental Dermatology
FC(A)	Finn Chambers (Aqua)
FM	Fibromyalgia
FM I	Fragrance mix I
FM II	Fragrance mix II
GSTS	Gold sodium thiosulphate
HEMA	2-Hydroxyethyl methacrylate
MCI/MI	Methylchloroisothiazolinone/methylisothiazolinone
MP	<i>Myroxylon pereirae</i>
OHIP-14	Oral Health Impact Profile-14
SCD	Systemic contact dermatitis
TNF	Tumour necrosis factor
VAS	Visual analogue scale

Abstract

The aim of this thesis was to assess whether contact allergy could be significant in chronic pain syndromes, using fibromyalgia (FM) as a model. Given our knowledge of the role of gold allergy in systemic contact dermatitis, a specific focus on gold allergy would form part of the project. Specific aims included assessing the prevalence and pattern of contact allergy in individuals with FM, assessing the clinical relevance of gold allergy in FM, and examining the oral status of individuals with FM.

Prevalence of contact allergy in FM was assessed with patch testing and comparing with control groups. Questionnaires were used to assess relevance of positive patch test reactions and quality of life in FM. A dental examination was used to assess the oral health of individuals with FM and compare with a population control group.

119 females with FM were recruited to the patch test studies. The FM group had an overrepresentation of contact allergy to nickel ($p = 0.0004$), *Myroxylon pereirae* ($p = 0.00004$) and Fragrance mix I ($p = 0.010$) compared with population controls. There were significantly more reactions to the Swedish baseline series in the FM group ($p < 0.0001$) than in population controls. Testing with an extended dental series showed a significantly higher prevalence of gold allergy in individuals with FM than in dermatitis controls ($p = 0.043$) and significantly more positive reactions for (meth)acrylates than a control group with oral symptoms ($p = 0.016$).

Significantly more participants with gold allergy reported cutaneous symptoms upon contact with gold compared with those who did not have gold allergy ($p = 0.010$). Gold contact allergy was also overrepresented in those with oral symptoms ($p = 0.024$). Visual analogue scores showed that those with oral symptoms and gold allergy scored significantly higher in the domains of pain, tiredness, and malaise.

FM individuals had a higher stage of periodontal disease than controls ($p = 0.017$) and a higher frequency of oral lesions ($p < 0.001$). The FM group reported poor oral health related quality of life scores.

The contact allergies overrepresented in FM include those where sensitisation may occur via the oral mucosa. Gold in particular is described in systemic contact dermatitis. Periodontal disease is associated with systemic inflammation. Contact allergy may play a role in poorer oral health and systemic inflammation in FM.

Popular science summary (*Populärvetenskaplig sammanfattning*)

Fibromyalgia (FM) is a chronic disorder, characterised by widespread muscular pain and hypersensitivity to sensory inputs. It is usually accompanied by a wide spectrum of symptoms including fatigue, sleep difficulties, gastrointestinal problems, and headaches. It is a common condition and is estimated to affect up to 2.3% of adults worldwide. The symptoms experienced in FM have a large impact on quality of life, with many sufferers experiencing reduced or no working capacity. The condition is much more common in women, and other risk factors include rheumatological diseases and psychological trauma. The causes of FM remain unknown despite research from many diverse specialist fields, but it has been shown that patients with FM have altered signalling in the nerve pathways that transmit and receive pain, described as 'central sensitisation.' This signalling may be affected by inflammation or stress within the body.

Contact allergy is an immune reaction where the body reacts upon contact with a specific substance ('allergen'). This can lead to development of eczema — dry and itchy skin. The allergy develops after initial exposure to the substance ('sensitisation'), and repeated contact thereafter causes reactivation of the immune system and an eczema. Common contact allergens include metals such as nickel, fragrances, and preservatives. Contact with allergens in the oral cavity can also cause sensitisation and oral inflammation. It is known that some contact allergens, particularly metals including gold and nickel, can also cause inflammation in the body in allergic individuals ('systemic contact dermatitis'). Symptoms can include rashes and pain in the joints and muscles. We investigate contact allergy through patch testing, where small amounts of the substance are applied to the skin, and evaluated by the dermatologist to assess if any reaction ensues. Constant collaboration is required between specialists to determine which allergens are currently prevalent and relevant, resulting in groups ('series') of allergens that are tested simultaneously in the individual patient. Mapping these allergens, and frequency of contact allergies in both the population and specific occupations or groups of patients, contributes to appropriate legislative measures to limit exposure to potentially harmful substances.

In this project we aimed to assess which contact allergies were common in the FM population and if they could be relevant in the symptoms experienced in FM.

In studies I and II we performed patch testing on 119 females with FM, and compared the results with the general population, patients with dermatitis, and patients with oral symptoms. Compared to the general population, the FM participants had more nickel allergy and more allergy to fragrance and flavouring substances. Compared to dermatitis patients, the FM group had more gold allergy,

and compared to patients with oral symptoms, the FM group had more acrylate allergies.

In study III, using a questionnaire, we found that individuals with FM and gold allergy experience skin problems when wearing gold jewellery and more oral problems than those without gold allergy.

In study IV we performed a dental examination and distributed a questionnaire on oral health to 60 of the FM individuals who had participated in studies I-III, and compared findings with the general population. We found that individuals with FM had more severe periodontal disease (gum disease), and more inflammatory oral disease than the general population. They also reported a high degree of oral symptoms and a poor oral related quality of life.

In conclusion, individuals with FM appear to have a high burden of allergy to substances where exposure, and therefore sensitisation, can occur in the oral cavity, namely dental materials, and fragrances (flavours) that are present in spices, foodstuffs, and other consumer products. Additionally, some aspects of oral health are poorer in FM than the general population. The particular allergies seen in FM are those that can cause generalised symptoms, and are a possible link with the systemic symptoms seen in FM. Periodontitis is also associated with systemic inflammation. There may be a complex relationship between contact allergy, oral disease and systemic inflammation in FM. Additional study is required to clarify these possible interactions, and whether reduced exposure to allergens in allergic individuals can alleviate some of the symptoms in FM. The results of this project can be an important first step in understanding potential causes of FM, which in turn can set a course for new treatments and preventative measures for this severely affected patient group.

Fibromyalgi (FM) är en kronisk sjukdom som kännetecknas av utbredd muskelsmärta och överkänslighet för sensoriska stimuli. Vid FM ses ofta ett brett spektrum av symtom, som trötthet, sömnsvårigheter, mag- och tarmbesvär och huvudvärk. FM är vanligt och uppskattas drabba upp till 2,3 % av den vuxna befolkningen världen över. FM har en stor negativ påverkan på livskvaliteten och många drabbade har nedsatt eller ingen arbetsförmåga. FM är betydligt vanligare hos kvinnor och riskfaktorer är reumatiska sjukdomar och psykologiska trauman. Trots omfattande forskning inom området är orsakerna till FM fortfarande okända men det är dock känt att patienter med FM har förändrad signalering i nervbanor som förmedlar och tar emot smärta, vilket beskrivs som 'central sensitisering'. Denna signalering kan påverkas av inflammation eller stress i kroppen.

Kontaktallergi är en immunologisk reaktion som ses när en individ blir allergisk mot ett specifikt ämne ('allergen'). När den som blivit allergisk åter kommer i kontakt med det allergiframkallande ämnet aktiveras immunsystemet och det bildas ett eksem med torr och kliande hud. Några av de vanligaste kontaktallergenerna är metaller som nickel, doftämnen och konserveringsmedel. Kontakt med allergener i munhålan kan ge upphov till allergi, lokaliserade besvär och inflammation i munnen. Det är känt att vissa kontaktallergener, särskilt metaller som guld och nickel, även kan orsaka inflammation i kroppen hos allergiska individer ('systemisk kontaktdermatit'). Symtomen kan inkludera utslag och smärta i leder och muskler. Kontaktallergi undersöks genom lapptestning, där standardiserade mängder av allergenerna appliceras på huden och därefter avläses testet av en hudläkare för att se om någon reaktion uppstått. Kontinuerligt samarbete mellan specialister krävs för att avgöra vilka allergener som för närvarande är vanliga och relevanta, vilket resulterar i grupper ("serier") av allergener som testas samtidigt hos den enskilda patienten. Kartläggning av dessa allergener och förekomsten av kontaktallergier i befolkningen eller särskilda yrkes- och patientgrupper bidrar till lämpliga lagstiftningsåtgärder för att begränsa exponering för potentiellt skadliga ämnen.

I detta projekt hade vi som mål att undersöka vilka kontaktallergier som var vanliga bland individer med FM, samt att se om det finns något samband mellan kontaktallergier och FM-symtom.

I studierna I och II utförde vi lapptestning på 119 kvinnor med FM och jämförde resultaten med allmänbefolkningen, patienter med eksem, samt patienter med symtom från munhålan. Jämfört med allmänbefolkningen hade studiedeltagarna med FM mer nickelallergi och mer allergi mot doft- och smakämnen. Jämfört med patienter med eksem hade FM-gruppen mer guldallergi, och jämfört med patienter med besvär från munhålan hade FM-gruppen mer akrylallergi.

I studie III, som var en enkätstudie, fann vi att individer med FM och guldallergi upplever hudproblem vid användning av guldsmycken samt mer orala problem än de utan guldallergi.

I studie IV genomförde vi en tandundersökning och delade ut en enkät om munhälsa till 60 av de FM-individer som deltagit i studierna I–III, och jämförde resultaten med allmänbefolkningen. Vi fann att individer med FM hade mer uttalad paradontit (tandlossning) och mer inflammatorisk sjukdom i munnen än allmänbefolkningen. De rapporterade också en hög grad av orala symtom och en sämre munhälsorelaterad livskvalitet.

Sammanfattningsvis verkar individer med FM ha en hög förekomst av allergi mot ämnen där exponering, och därmed sensibilisering, kan ske via munhålan, såsom ämnen i dentala material och doftämnen (smakämnen) som finns i kryddor, livsmedel och andra konsumentprodukter. Dessutom är vissa aspekter av munhälsan sämre vid FM jämfört med befolkningen i stort. De specifika allergier som ses vid FM är sådana som kan orsaka generaliserade symtom och därmed utgöra en möjlig koppling till de systemiska symtom som ses vid FM. Parodontit är också associerat med systemisk inflammation. Det kan finnas ett komplext samband mellan kontaktallergi, orala sjukdomar och systemisk inflammation vid FM. Ytterligare studier krävs för att klargöra dessa möjliga samband och om minskad exponering för allergener hos allergiska individer kan lindra vissa av symtomen vid FM. Projektets resultat kan vara ett första viktigt steg mot att förstå möjliga orsaker till FM vilket i sin tur kan bana väg för nya behandlingar och preventiva åtgärder för denna drabbade patientgrupp.

Preface

“I should be pleased to have the question solved, why some handle with impunity what will so soon severely punish others. Can it be possible, that some peculiar structure of the cuticle, or rete mucosum, constitutes this idiosyncrasy?”

R. Dakin, Remarks on a Cutaneous Affection, produced by certain Poisonous Vegetables, 1829 (1).

For this PhD student, contact allergy remains almost as much an enigma as it was for Dr R Dakin in the 19th century. The detective work that is routinely performed by the physicians and chemists in the contact allergy clinic in order to uncover occasionally unusual contact allergens and routes of sensitisation resulting in complex clinical presentations is challenging and often involves a degree of head-scratching before a unifying explanation for the patient’s difficulties is found. However, the elegance of the ‘treatment’ — preventing exposure to the culprit allergen — is rewarding for the clinician and can be life-changing for the patient. This is what drew me to this project on contact allergy and fibromyalgia — could dermatologists contribute one or two pieces to the complex puzzle of this chronic pain syndrome?

The initial, somewhat surprising results of the survey assessing contact allergy in fibromyalgia gave impetus to the doctoral project. Fibromyalgia appears to be associated with a specific contact allergy profile. In analogy with our daily work with contact dermatitis patients, the search for explanatory mechanisms for this pattern of contact allergy in fibromyalgia has been complex and will continue to challenge the researcher. However, there remains potential for great impact in relieving some of the disease burden in this patient group who experience significant quality of life impairment.

Introduction

The inspiration for this doctoral project originates primarily in research into gold contact allergy that has been conducted over the last four decades at the Department of Occupational and Environmental Dermatology (DOED) (*Yrkes- och miljödermatologisk avdelning*), Malmö, Sweden. Accumulated evidence demonstrates that contact allergy to gold can manifest systemically, with dermatitis, arthralgia, and malaise (systemic contact dermatitis). This knowledge led ultimately to the novel hypothesis that contact allergy may explain symptomology in individuals with chronic pain in the absence of identified biomechanical or inflammatory diagnoses, such as in fibromyalgia (FM). Given the paucity of research into systemic contact dermatitis and contact allergy in FM, a dynamic approach to the project was required, with initial study findings informing the subsequent pathway of investigation.

The pattern of contact allergy subsequently demonstrated in the first phase of the project, a survey of contact allergy in the FM population, required a widening in the scope of the project to assess the role of the oral cavity in contact allergy in FM, a study undertaken in collaboration with colleagues from the Public Dental Service (*Folktandvården*), Skåne, Sweden.

Combined findings from these studies have stimulated discussion on the potential interplay between contact allergy, oral health and systemic inflammation in FM. This introduction will detail the mechanisms and investigation of contact allergy, as well as discussing a selection of contact allergens that have relevance to the doctoral project. Summaries of both fibromyalgia and aspects of oral health are also included.

Allergic Contact Dermatitis

Contact allergy is a reaction pattern defined as an immunologically acquired delayed hypersensitivity that is invoked upon contact with a particular substance. When sufficiently exposed after sensitisation, the usual resulting clinical manifestation of this process is allergic contact dermatitis (ACD), which presents as an eczematous dermatitis with itch, erythema, vesicles, and scaling. Common substances causing ACD include metals such as nickel, fragrances, preservatives, and hair dyes. Contact

allergy is very common with an estimated prevalence of 27% in the European population (2).

To achieve a clinical allergic contact dermatitis, several conditions need to be fulfilled:

Exposure to a substance (allergen) capable of inducing a delayed hypersensitivity reaction.

Sensitisation of the immune system to said allergen.

Elicitation of a hypersensitivity reaction upon repeated exposure to the allergen, with immunological activation and resultant dermatitis (figure 1).

Allergens

Contact allergens are small molecules with the capability of penetrating the stratum corneum and thus stimulating the cascade of events that ultimately leads to a contact allergy. These molecules in their base form are more correctly known as haptens and become capable of eliciting an immune response only upon binding to a host protein or amino acid (haptensisation). Some substances require additional chemical transformation, for example, oxidation prior to skin penetration (prehaptens), while others undergo activation via the host metabolism after entering the skin (prohaptens). Metals are able to activate the immune system directly by binding to histidine on toll-like receptor 4 expressed on cell surfaces (3).

Sensitisation

The process of sensitisation takes days to weeks, and can occur with both *de novo* or chronic exposure to an allergen (4). Cell types that are involved in the sensitisation process include keratinocytes and dendritic cells. Keratinocytes confer the barrier function of the skin through physically blocking skin penetration of foreign substances including haptens, and preventing egress of water through the epidermis. They also have an active role in the innate immune system, releasing inflammatory mediators including interleukin-1 β (IL-1 β) and tumour necrosis factor (TNF) upon binding of haptens to toll-like receptors on the cell surface.

Dendritic cells (DCs) are also known as antigen presenting cells. They have several subtypes, including epidermis-residing Langerhans cells and dermal dendritic cells. They can be directly activated by haptens or by cytokines released in the creation of the inflammatory milieu by activated keratinocytes. Upon activation, DCs both release pro-inflammatory cytokines, thus perpetuating the inflammatory cascade locally in the skin, and migrate to the skin-draining lymph nodes. As the DCs mature, they express the specific hapten on the cell surface via the major histocompatibility complex (MHC) class I and II (5). In the lymph nodes, the DCs

encounter hapten-specific T cells, causing clonal expansion of effector and memory T cells. The sub-group of memory T cells that migrate to and subsequently patrol the skin are known as skin resident memory T cells (5-7).

Elicitation

The process that results in the clinical manifestations of ACD is more rapid than the sensitisation phase and occurs upon re-exposure to the hapten, either via the skin or systemically. Hapten-specific memory T cells are activated directly, and local release of inflammatory mediators in response to the hapten exposure also facilitates migration of additional hapten-specific T cells to the skin. Activated T cells proliferate upon activation and have different effector roles according to subtype, including direct cytotoxicity, recruitment of other inflammatory cells including macrophages, mast cells, and eosinophils, and facilitation of keratinocyte apoptosis. The resulting loss of cohesion within the epidermis contributes to the clinical picture of desquamation and oedema in ACD (5,8).

Cross-reactivity can occur in the elicitation phase if there is exposure to a hapten that is structurally similar to one to which the individual previously has been sensitised (4).

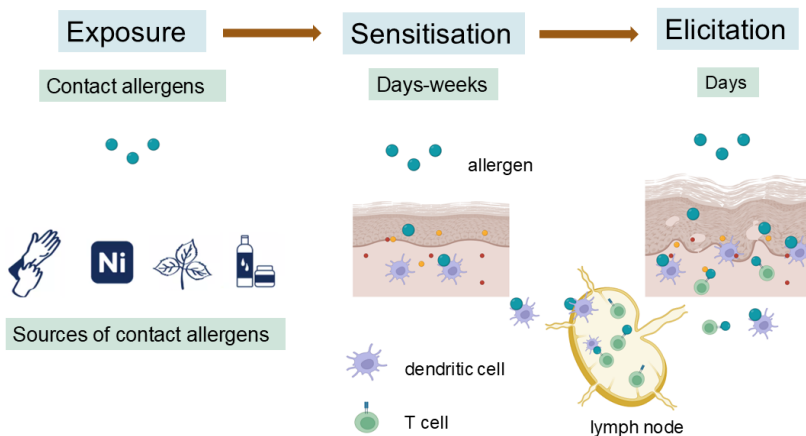


Figure 1: The process of allergic contact dermatitis.

Diagnosis of allergic contact dermatitis

Patch testing

The standard procedure for diagnosis of contact allergy is patch testing. The aim of the test is to reproduce the elicitation phase of a contact allergic reaction. By using standard concentrations and doses in mg/cm² of allergen and a calibrated method of test reading, reproducibility and reliability are achieved.

Patch test systems consist of small chambers that are mounted on tape. The test allergens are dispersed in a vehicle (commonly water or petrolatum), added to the chambers, and the system is then usually applied to the upper back of the patient (9). This method of occlusion facilitates cutaneous penetration of the allergen. It is recommended that the occlusion time is 48 hours, which is more than adequate for elicitation of contact allergic reactions with standard test preparations. A multitude of standard test preparations are available, and several test chamber systems which differ in chamber size and material are in current use. Pre-loaded test systems are also available, with the TRUE Test system being the most widely used, where allergens are loaded onto a hydrophilic gel matrix. The TRUE Test system has been validated through comparison with conventional patch testing with aluminium chambers ('Finn Chambers'), with good correlation demonstrated between the different methods (10). Test substances can also be prepared from the patient's own materials if required (9).

Two readings of patch tests are recommended; at day (D) 3 or D4 and then D7 after test application. D4 readings trace the most contact allergy but a second reading is required because some substances tend to later reactions (including antibiotics, corticosteroids, (meth)acrylates, and gold) (9,11).

Evaluation of patch test reactions is performed by a clinician according to the international criteria established by the International Contact Dermatitis Research Group (9,12) (table 1). Morphologically positive reactions present at least one of the test readings are deemed to be contact allergic reactions. As interpretation is performed by individual clinicians, inter-observer variability can occur, particularly in the case of doubtful or irritant reactions (13). Additionally, the criteria may be difficult to apply in darker skin types (14). The test outcome can also be influenced by site of testing, skin irritation, and medications (4,9). Seasonal variability in patch test reactions can also occur, and reproducibility of positive patch test readings can vary over time (15,16).

Patch testing is time consuming, necessitating several clinical attendances by the patient, but is a safe and well tolerated procedure. Potential adverse effects include prolonged test reactions, particularly in the case of gold, a flare of an ACD, or an active sensitisation to a test substance (9). Active sensitisation is defined as a reaction occurring 10 or more days after testing, with a subsequent early (D3-4)

reaction upon retesting suggesting the diagnosis (9,17,18). However, active sensitisation is very rare (19).

Table 1: Description of patch test reactions according to the second and proposed third International Contact Dermatitis Research Group Classification of patch test reactions (12).

Patch test reaction	Morphology	
Negative (-)	No reaction, or hardly discernible from surrounding skin.	
Doubtful (+?)	Erythema/infiltration/papules exceeding that of surrounding skin but not fulfilling the minimum criteria for an allergic reaction.	
Allergic reaction- weak (+)	Erythema and infiltration covering the whole test area, possibly few papules.	
Allergic reaction- moderate/strong (++)	Erythema and infiltration covering the whole test area, many papules, possible vesicles.	
Allergic reaction- strong (+++)	Erythema and infiltration covering the whole test area, many vesicles, possible coalescence to bullae.	
Irritant reaction (IR)	Dry skin, scaling, pustules, erosions.	

Patch test series

Clues in the patient history and examination, for example occupational exposure, timing of cutaneous reactions, and the distribution of eczema, can guide the clinician as to which culprit allergens may play a role in a potential ACD. This is of course easier with well-established and common contact allergens. With less ubiquitous allergens or unclear routes of exposure it is much more difficult to identify causative allergens. It is therefore recommended that all individuals with a suspected ACD are tested with a standardised ‘baseline series’ of allergens.

The composition of a baseline series must be continually reviewed and modified according to population exposures, emergence of new contact allergens, and decreasing exposure to established allergens due to, for example, legislative measures or declining use of (or exposure to) certain substances. Inclusion in a series is based upon prevalence of allergy identified through patch testing and if the allergen has a high exposure profile or significant clinical relevance. In Sweden the Swedish baseline series is recommended and is updated yearly (20). The baseline series may also be complemented with additional substances, according to local routines and exposures, as well as the patient’s personal exposure profile. To allow for ease of testing, allergens are sometimes combined into one preparation, such as with fragrance mixes.

Establishing relevance of positive reactions in patch testing can be challenging. A clear picture, via detailed appraisal of the patient history, needs to be obtained regarding current or previous exposures to the relevant allergen and whether this exposure can account for the patient's clinical presentation.

Systemic contact dermatitis

Systemic contact dermatitis (SCD) is characterised by symptoms that can occur when an individual sensitised to an allergen is exposed to the same allergen via a systemic route (21). Possible modalities of exposure are manifold and can include oral or transmucosal routes, or via medical implants (22,23). SCD can have a diverse clinical presentation including rash at previous sites of ACD, hand dermatitis, and flexural eruptions (23-25). Generalised symptoms such as headache, malaise, and arthralgia have also been observed upon oral provocation in sensitised individuals (25,26). There is evidence that the mechanisms of SCD include T-cell mediated immune reactions specific to the particular allergen in question, with reactivation of previous positive patch test sites upon controlled systemic administration of allergens including corticosteroids, nickel, and gold (27-29). However, it is likely that other inflammatory and immune mechanisms are also contributory and that these can vary dependent on the specific allergen. For example, certain medications may interact directly with T-cell receptors leading to activation of the immune cascade in the absence of a prior sensitisation process (30).

The heterogeneous nature of systemic allergen exposure and absorption, immune activation, and subsequent clinical presentation mean that both clinical investigation and research into SCD are challenging. In contrast to investigation of ACD, there is no standardised testing procedure or marker of the diagnosis. Where exposure to an allergen is transient and high, such as with intravenous medications, a causal relationship between exposure and symptoms can be easier to demonstrate. Where there is a chronic exposure to low volumes of circulating allergen, such as with dental metals (gold and nickel) or food allergens (again nickel, spices, *Myroxylon pereirae*), the clinical index of suspicion for SCD is likely to be much lower and a cause-and-effect relationship more difficult to prove. Provocation studies, including administration of nickel and medicaments, have served to provide a proof of concept (21,25), but the value of elimination of the contact allergen in the form of exclusion diets or removal of metal prostheses appears to have variable results and is mainly limited to case reports and a few prospective trials (31-34).

SCD continues to present challenges for the clinician and the researcher. It is still not known why certain allergens are more implicated in SCD than others, particularly in the case of medications, and why only a minority of individuals with a specific contact allergy develop a subsequent SCD. The minimal eliciting dose

required to provoke SCD appears to be highly variable and may depend on both properties of the allergen and unexplored individual characteristics, including genetic factors and co-morbidities. Further details on SCD related to gold and fragrances are discussed in the next section on specific contact allergens.

Some notes on specific contact allergens

Gold

Gold is a metallic element, most commonly found in its pure ('native') form in nature in veins or alluvial deposits (35,36). It is classified as a precious metal due to its rarity and therefore high economic value, and can be considered a universal symbol of prosperity and achievement. Its consistent high value has conferred its use as currency, first as coinage and now on the trading floor; gold is still held in physical reserves by federal banks. The extensive use of gold within jewellery allows a personal and overt expression of wealth.

Properties of gold

Gold is a noble metal; in its metallic ground state it is chemically inert, being resistant to oxidative and corrosive processes. It is unreactive to alkalis and most strong acids, apart from 'aqua regia', a combination of hydrochloric and nitric acids, where the nitric acid acts as a strong oxidising agent (35,37).

Metallic gold is highly malleable and ductile (37). In practical usage, it is often combined with other metallic elements in alloys in order to increase strength and reduce costs. 'Yellow gold' is often an alloy of gold and copper, while in 'white gold' metals such as nickel or palladium are combined with gold (4). The purity of gold is defined by the carat (karat in USA) scale, where 24 carats denote pure gold (35).

Gold has several oxidation states of which I (Au (I), the aurous ion) and III (Au (III), the auric ion) are the most common. Au (I) forms compounds with ligands including sulphur-containing thiolates (for example, sodium aurothiomalate) or, in the human body, amino acids containing a thiol group such as cysteine or histidine (38-41). Au (III) is seen in the oxidising agent gold (III) chloride.

Medical applications of gold

- **Chrysotherapy:** Gold compounds have been used in the treatment of inflammatory disorders and infections since the 1890s (36). Sodium aurothiomalate and other gold salts were previously used extensively in the treatment of rheumatoid arthritis and cutaneous disorders including

pemphigus. However, due to an extensive side effect profile, including dermatitis and nephrotoxicity, and the development of safer alternatives including biological medications, the use of gold compounds has declined dramatically in recent years (36).

- **Prostheses:** Metallic gold, both pure and in combination (alloy), has been employed extensively in dental restorations due to its corrosion resistance, biocompatibility, and malleability (37). It has also been used as a coating for coronary stents and as an implant in lid-loading for individuals with lagophthalmos (36,42,43).
- **Colloidal gold:** Nanoparticles (1-100nm) of gold suspended in fluid are employed as biological probes in electron microscopy and as delivery systems for targeted medical or gene therapy (36).

Gold as a contact allergen

The journey to establishing gold as a contact allergen capable of eliciting an ACD has been somewhat convoluted and not without controversy. As elemental gold is inert it has little sensitising potential, which could lead one to discount the possibility of gold being an allergen. However, metallic gold oxidises upon exposure to fluids including sweat and saliva, a process probably facilitated by sulphur-containing amino acids including cysteine and histidine. The resultant gold ions bond to amino acids within the epidermis, completing the haptenisation process (38-41,44). Gold alloys have been shown to corrode more readily than high-carat gold, giving a greater potential for sensitisation and elicitation of contact allergic reactions (44).

Metallic gold is unsuitable as a patch test preparation due to its inert properties. Various gold salts including gold trichloride and gold sodium thiomalate have previously been employed, but irritant reactions have been described (45,46). Gold sodium thiosulphate (GSTS) has subsequently been identified as a suitable preparation for testing; it has a detection rate that is potentially higher than gold trichloride and does not give irritation reactions (45-47). GSTS 2.0% (w/w) in petrolatum is a commercially available hapten and has been used in the American Contact Dermatitis Society Core Allergen Series since 2013 (48). GSTS 0.075 mg/cm² is included in the preloaded TRUE test core panel (SmartPractice, Phoenix, AZ, USA).

Gold, in common with other metals, can give rise to late reactions that arise after the recommended D7 reading, and can persist for weeks or even months (49-51). The delayed nature of these reactions does not indicate active sensitisation in the case of gold, with late reactions also occurring upon re-testing of gold-allergic individuals (18). Testing with serial dilutions of gold also confirms 'true' allergy to gold, with reactions to low concentrations occurring late in individuals with confirmed gold allergy (18) (figure 2).

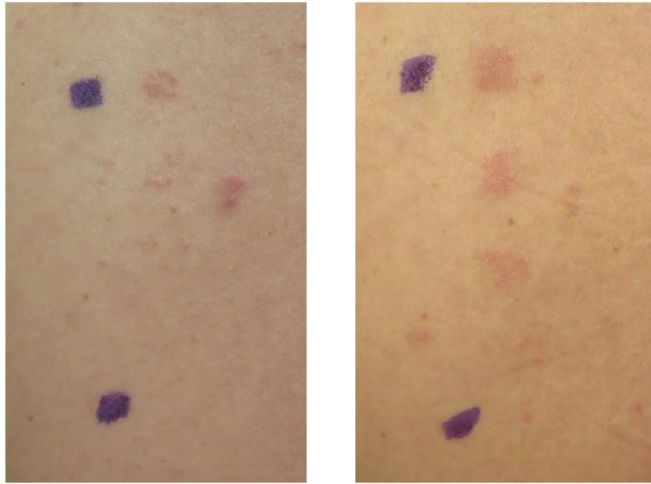


Figure 2: Positive test reactions to dilution series of gold sodium thiosulphate (GSTS).

Readings of the same patient at day 7 (left) and day 14 (right) showing late contact allergic reactions to low concentrations of GSTS. Photographs: Katharine Hopkins.

Due to variations in test preparation and timings of test reading, the exact prevalence of positive patch test reactions to gold is difficult to ascertain, with prevalences of 3.2-18.5% reported in dermatitis patients (52-54). A meta-analysis of 16 studies showed a pooled prevalence in dermatitis patients of 14.1% but emphasised the heterogeneity of studies included in the analysis (55). Whether gold allergy is of clinical relevance has been difficult to establish. Exposure to metallic gold in the form of jewellery is ubiquitous in the population, but adverse reactions to metallic gold in the form of dermatitis are rare, and mainly limited to case reports; most individuals with gold allergy tolerate the wearing of gold jewellery (51,56,57). A randomised study demonstrated that gold-allergic individuals provoked topically with gold earrings were significantly more likely to develop dermatitis than those provoked with titanium (58). Accumulated evidence suggests that gold allergy can be of significance in several clinical scenarios, as follows:

- **Dental implants:** Oral gold is associated with systemic gold exposure, with blood gold levels correlating with the burden of dental gold (59). There is also an association between the number of gold surfaces and gold allergy (60-62). Intra-oral pathologies such as lichen planus and stomatitis may be related to dental gold (63,64).
- **Endovascular implants:** Systemic release of gold from gold-coated coronary stents has been shown, with individuals with gold stents having higher blood gold levels than those with nickel stents (65). Gold stents were correlated with gold contact allergy, and gold levels were positively

correlated with strength of patch test reaction in the gold-stented individuals (65,66). Gold-allergic individuals with gold stents had an increased frequency of coronary artery restenosis (67).

- **Systemic contact dermatitis:** Controlled randomised provocation studies have demonstrated that gold-allergic individuals can react to systemic (intramuscular) administration of gold, with rashes, constitutional symptoms, reactivation of positive patch test reactions, and elevation of pro-inflammatory cytokines (28,68,69). That strength of patch test reaction to gold is correlated with blood gold level as described above also gives evidence for the role of gold as a systemic contact allergen (65). There are anecdotal case reports supporting the importance of gold giving rise to SCD: A patient developed a widespread dermatitis and malaise upon administration of a homeopathic preparation containing gold 5 µg/mL and was subsequently found to be allergic to gold. Full symptom resolution was obtained upon cessation of the preparation (70). Another individual with gold allergy had continued flares of oral lichenoid reactions at sites of previous dental gold after treatment with a gold coronary stent (71).

It is therefore recommended to consider patch testing with gold in the presence of symptoms potentially related to either localised or systemic exposure to gold.

Fragrances

Fragrances are chemical substances that can either occur naturally or be produced synthetically. Due to their pleasant scent, they have a diverse range of applications including cosmetics, household products, and as flavouring substances (72). As there is almost universal exposure to products containing fragrances and the skin is usually in direct contact with these products, they are among the most commonly reported contact allergens. A general European prevalence of fragrance allergy of 4.7% was reported in a population study conducted in 2008-11 (73). Multiple fragrances have been identified as contact allergens, and within the EU, 26 of these must be declared if present at certain levels in cosmetic products (increasing to 82 in July 2026) (73,74). The most common clinical manifestation of fragrance allergy is as an ACD, and SCD has also been reported (32,75). However, as a single perfume may contain multiple components, identification of specific causative allergens can be difficult.

Fragrance mixes I and II

To allow for ease of testing in baseline series, mixtures of fragrances are employed as patch test preparations. The composition of these mixtures is listed in table 2. Fragrance mix I (FM I) has been used in the European baseline series since the 1970s and fragrance mix II (FM II) was added in 2005 in order to increase the detection rate of fragrance allergy (76,77). Prevalence of sensitisation to FM I and

FM II in European dermatitis patients has been shown to be 6.81% and 3.64% respectively (78). Testing with the substances separately can be considered if clinically indicated in certain cases (79,80). Certain ingredients in both fragrance mixes are used in the food industry as flavour substances. Those of importance in FM1 (and in common with *Myroxylon pereirae*, see below) are illustrated in figure 3. In addition, eugenol is found in dental antiseptics and dental impression and restorative materials (81).

Table 2: Fragrance mix I and II composition, European baseline series.

All test preparations are in petrolatum.

Fragrance mix I (Concentration %)	Fragrance mix II (Concentration %)
Amyl cinnamal (1.0)	Citral (1.0)
Cinnamal (1.0)	Citronellol (0.5)
Cinnamyl alcohol (1.0)	Coumarin (2.5)
Eugenol (1.0)	Farnesol (2.5)
<i>Evernia prunastri</i> (Oakmoss) absolute (1.0)	Hexyl cinnamic aldehyde (5.0)
Geraniol (1.0)	Hydroxyisohexyl 3-cyclohexane carboxaldehyde (2.5)
Hydroxycitronellal (1.0)	
Isoeugenol (1.0)	
Sorbitan sesquiolate (1.0) ^a	

^aUsed as an emulsifier.

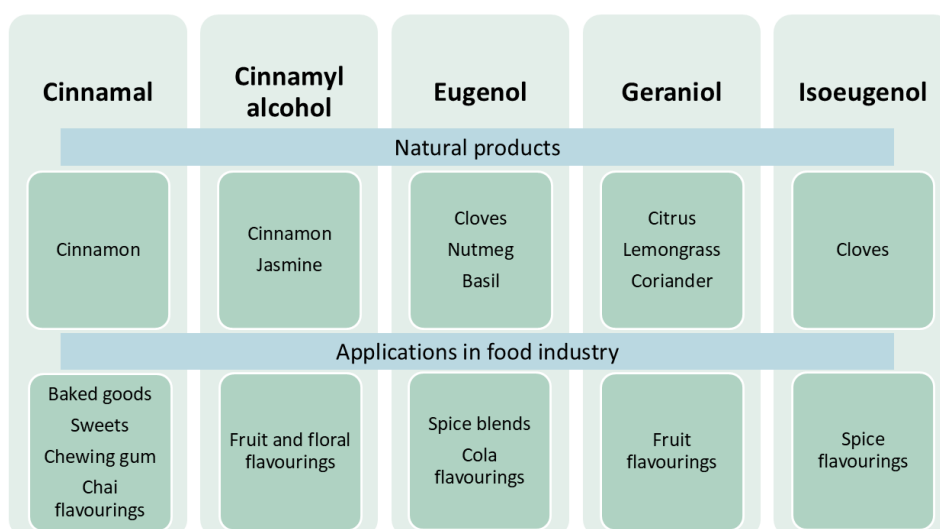


Figure 3: Constituents of fragrance mix I and *Myroxylon pereirae* commonly used in the food industry as flavour substances (82-86).

Myroxylon pereirae

Myroxylon pereirae resin (MP, Balsam of Peru) is also included in the European and Swedish baseline series. MP is obtained from the bark of the tree *Myroxylon*

balsamum (L.) Harms var. *pereirae* (Royle) Harms which grows mainly in El Salvador. The work of Professor Niels Hjørrth (1919-1990) established MP as an indicator of fragrance allergy, with the demonstration that patients with contact allergy to MP also reacted to cosmetics and topical pharmaceuticals (87). MP is tested at 25% in petrolatum in baseline series, and remains one of the most common contact sensitizers with a prevalence of 6.6% (Europe, 2019-2020) to 7.4% (North America, 2019-2020) in dermatitis patients (88,89).

The composition of MP is not wholly defined due to different methods of analysis and sampling of different fractions or derivatives but several hundred chemicals have been identified, with the highest concentrations being the contact allergens benzyl cinnamate and benzyl benzoate, and cinnamic acid, derivatives of which are also contact allergens (90,91). Uses of MP are wide-ranging; it has been used since the 17th century as a topical medicament due to purported antiseptic properties, within dental products, in commercial food production to confer both aroma and taste, and as a fragrance it has been used in the cosmetic industry. Use within pharmaceuticals has now declined due to both high rates of contact allergy to MP and the availability of better alternative antiseptics (92) (figure 4). Use of unrefined MP in cosmetics was banned by the International Fragrance Association in 1982, with use limited to extracts and distillates of MP with a total level of 0.4% in cosmetic products (93).

In terms of allergens found in MP, those of importance include, among others, the fragrances isoeugenol, eugenol, and cinnamyl alcohol. Individuals with positive patch test reactions to MP are therefore likely to have been sensitised to these allergens via fragranced products, with MP acting as a marker of fragrance allergy (93). Simultaneous reactions to MP and FM1 are common due to presence of allergens common to both preparations (figure 3) (76).

MP is not only used in commercial preparations; allergenic components of MP occur naturally in spices such as cinnamon (cinnamal) and cloves (eugenol), and other foods such as citrus and tomatoes (94). These foods can also contain cross-reactors or metabolites of allergens present in MP (90). Systemic contact dermatitis has been described in connection with ingestion of spices in individuals with MP allergy but the value of elimination diets in resolution of symptoms is still uncertain (31,32,87,90,95).

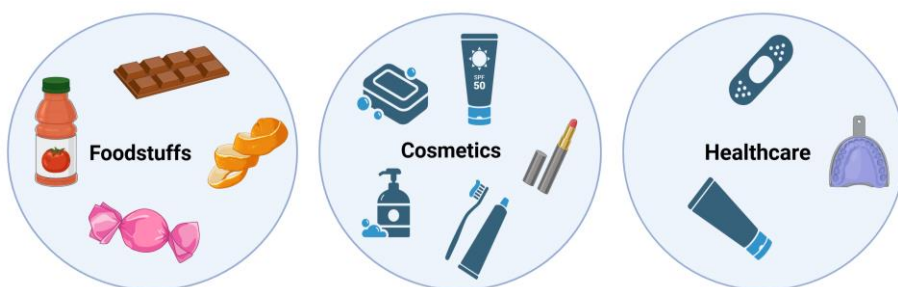


Figure 4: Industrial uses of *Myroxylon pereirae*.

(Meth)acrylates

(Meth)acrylate (acrylic) plastics are materials formed from the polymerisation of monomeric esters and other derivatives of acrylic acid and methacrylic acid. The resulting products have a myriad of uses due to their lightweight and durable properties, and exposure to acrylics is therefore almost inevitable in daily life (table 3) (4,96). The polymerised end products are considered to be inert and are therefore not hazardous to the skin. However, the base monomers and other chemicals that are used in the production of the substance are reactive, and many are established contact sensitisers. Residual monomers can persist in the end products.

Table 3: Common uses of (meth)acrylates(4,97).

Application	Examples
Industrial products	Adhesives UV-curable inks and coatings Fibreglass Paints and lacquers Pipe relining material
Medical products	Adhesive tape Bone cement Electrodes Hearing aids Implantable medical devices
Dental products	Dental prostheses Orthodontic adhesives Restorations
Consumer products	Fitness devices Glues Spectacle frames Headphones Hygiene products (nappies, pads)
Cosmetics	Nail cosmetics Glue for eyelash and hair extensions

Acrylate monomers consist of an alkene (vinyl) group conjugated with a carbonyl-containing ester functional group (figure 5). The carbon-carbon double bond is highly reactive and enables polymerisation. The ester linkage connects to a functional side chain ('R') which confers physical properties including adhesion. Methacrylates contain an additional methyl group on the alkene carbon which leads to lower reactivity and therefore a lower sensitising capacity (4).

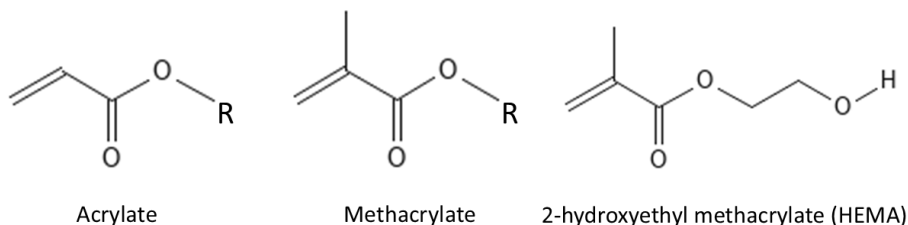


Figure 5: Schematic structure of acrylates and methacrylates.

R = Functional side group.

Polymerisation is achieved via initiators which are activated chemically, thermally, or via UV or visible light to form free radicals that break the carbon double bonds of the monomers which then link in long chains. After polymerisation, the resulting material is processed and shaped into the final product. In addition to the component monomers, the initiators, catalysts, and inhibitors which used in this process can also act as sensitisers. Residual monomers can also be present after the curing process (4,96).

Due to the similarities of chemical structure, significant cross-reactivity occurs between many (meth)acrylates, and concomitant sensitisation can also occur (98). Exposure to incompletely polymerised (meth)acrylates increases the risk of sensitisation and therefore (meth)acrylate allergy is most often occupationally related, including among nail technicians, dental workers, and industrial workers (11,99-101). Common patterns of clinical presentation include hand eczema, pulpitis, and nail dystrophy (101).

Changes in the pattern of (meth)acrylate use and the emergence of new allergens have led to a changing pattern in presentation of (meth)acrylate related contact dermatitis in recent times. Aside from case reports on products such as earphones and mobile phone screen protector glue, increasing consumer use of (meth)acrylate-containing nail products has led to increased allergy to (meth)acrylates among consumers as well as nail technicians (101-106). Another important emerging source of sensitisation to (meth)acrylates is via implantable medical devices such as continuous glucose monitors and insulin pumps, which can ultimately lead to discontinuation of the device and resultant morbidity (107,108).

2-hydroxyethyl methacrylate (HEMA) 2.0% in petrolatum has been used in the European baseline series since 2019 for routine testing, and is included in the supplementary series tested at the DOED in Malmö (figure 5). It is considered to be an appropriate marker for (meth)acrylate allergy, with a sensitivity of 90% in patients sensitised to dental materials and nail products (11,98). Prevalence of positive reactions to HEMA in the European baseline series is reported at 2.3% (Europe, 2019-2020) (88,109). Within the EU the use of HEMA has been restricted to nail products intended for professional use due to the high prevalence of contact allergy, but such products remain easily accessible for purchase by non-professionals (88,97).

Fibromyalgia

Fibromyalgia (FM) is a chronic condition characterised by widespread pain for which no alternative cause can be identified (110,111). The term ‘fibromyalgia’ has been in use since the 1970s but the concept of widespread muscular pain is described in the medical literature as early as 1904 (110,112,113). The pain is often accompanied by fatigue, cognitive dysfunction, other somatic symptoms, and psychiatric illness including depression and anxiety (112-114).

The prevalence of FM is reported as between 2-3% worldwide, but estimates vary according to diagnostic criteria used (115). The majority of studies estimating prevalence have been performed in Europe and North America. A higher prevalence is reported in women, but this may be due to application of previous diagnostic criteria (115,116). The burden of disease in FM results in not only a generally poorer quality of life for the individual, but also societal impact due to reduced work capability and health care costs (117,118). Studies assessing the prognosis in FM demonstrate the condition is ultimately chronic, with symptoms that pervade and fluctuate through life (119,120).

Diagnosis of FM

FM is a clinical diagnosis; to date no biomarker has been identified as an aid to diagnosis or monitoring of the condition (111,115,121). Standardised criteria for the diagnosis of FM were first approved in 1990 by the American College of Rheumatology (ACR) and included both a history of widespread pain and presence of specific tender points. However, the physical examination was found to have poor validity and reproducibility, hence revision of the diagnostic criteria both in 2010/2011 and 2016, the latter with the aim of refining the description of generalised pain and merging physician and patient symptom criteria (110,113,122,123). The 2016 criteria also highlight the validity of FM as a diagnosis even when coinciding

with other diagnoses with chronic pain as a feature (123). The current ACR diagnostic criteria for FM are summarised in figure 6.

FIBROMYALGIA DIAGNOSIS The following three are met: 1. Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) ≥ 5. OR WPI 4-6 and SSS ≥ 9 2. Generalised pain: Pain in at least 4 of 5 regions. 3. Symptoms have been generally present for at least 3 months. A diagnosis of FM is valid irrespective of other diagnoses. A diagnosis of FM does not exclude the presence of other clinically important illnesses.	Widespread Pain Index (WPI) The number of areas in which the patient has had pain over the last week (Score 0-19 points). ^aNot included in generalised pain definition <table> <tr> <td>Left upper region</td><td>Right lower region</td></tr> <tr> <td>Jaw^a</td><td>Hip</td></tr> <tr> <td>Shoulder girdle</td><td>Upper leg</td></tr> <tr> <td>Upper arm</td><td>Lower leg</td></tr> <tr> <td>Lower arm</td><td></td></tr> <tr> <td>Left lower region</td><td>Axial region</td></tr> <tr> <td>Hip</td><td>Neck</td></tr> <tr> <td>Upper leg</td><td>Upper back</td></tr> <tr> <td>Lower leg</td><td>Lower back</td></tr> <tr> <td></td><td>Chest^a</td></tr> <tr> <td></td><td>Abdomen^a</td></tr> <tr> <td>Right upper region</td><td></td></tr> <tr> <td>Jaw^a</td><td></td></tr> <tr> <td>Shoulder girdle</td><td></td></tr> <tr> <td>Upper arm</td><td></td></tr> <tr> <td>Lower arm</td><td></td></tr> </table>	Left upper region	Right lower region	Jaw ^a	Hip	Shoulder girdle	Upper leg	Upper arm	Lower leg	Lower arm		Left lower region	Axial region	Hip	Neck	Upper leg	Upper back	Lower leg	Lower back		Chest ^a		Abdomen ^a	Right upper region		Jaw ^a		Shoulder girdle		Upper arm		Lower arm	
Left upper region	Right lower region																																
Jaw ^a	Hip																																
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Symptom Severity Score (SSS) (0-12 points): For each of the three symptoms, indicate the level of severity over the past week (Score 0-9 points). • Fatigue • Waking Unrefreshed • Cognitive Symptoms 0= No problem 1= Slight or mild problems, mild or intermittent 2= Moderate, considerable problems, often present 3= Severe: pervasive, continuous, life-disturbing problems PLUS The sum of the number of the following symptoms the patient has been bothered by during the previous 6 months (Score 0-3 points). • Headaches • Pain or cramps in lower abdomen • Depression																																	

Figure 6: Fibromyalgia diagnostic criteria.

Adapted from the revised American College of Rheumatology fibromyalgia diagnostic criteria 2016 (123).

Pathogenesis

A multitude of hypothetical causative mechanisms have been explored in FM, the majority via experimental studies. It is likely that FM consists of a complex interplay between different contributory factors which can vary between individuals. These relationships are illustrated in figure 7.

Accumulated evidence suggests that the pain experienced in FM is *nociceptive* pain, defined as pain arising from the altered function of pain-related sensory pathways in the peripheral and central nervous systems. The mechanism behind this pain is described as *central sensitisation* whereby the central nervous system becomes overly sensitive to sensory stimuli, including pain signals. Over time, pain sensations become amplified, even when there is little or no tissue damage. *Hyperalgesia* — increased experience of pain to normally painful stimuli, and *allodynia* — pain response to normally non painful stimuli, are commonly experienced with central sensitisation. Evidence for central sensitisation has been demonstrated with changes in brain morphology and functioning seen on MRI examination, as well as assessing responses to experimental stimuli (124-126). Increase in excitatory neurotransmitters has been observed, with increased substance P in cerebrospinal fluid of FM individuals, as well as increased brain levels of glutamate (127,128). A reduction in inhibitory neurotransmitters (serotonin, noradrenaline, and dopamine) has also been recorded (129).

Additional potential contributory factors in the pathogenesis of FM include genetic disposition, with studies demonstrating familial clustering of FM diagnosis and association with genes involved in pain signalling (130-132). Peripheral mechanisms such as small fibre neuropathy (133) have been proposed. Multiple authors have explored the hypothesis that FM can be caused or exacerbated by a chronic systemic inflammation, with some evidence of an association of pro-inflammatory cytokines with FM, although a causal relationship has not been established (134-137).

There is a bidirectional relationship between psychosocial and cognitive factors and symptomatology of FM. Somatic responses to stress and affective illness include autonomic dysfunction, production of inflammatory mediators and alterations in central processing of pain, fuelling the ‘central sensitisation’ process as outlined above (112,138,139).

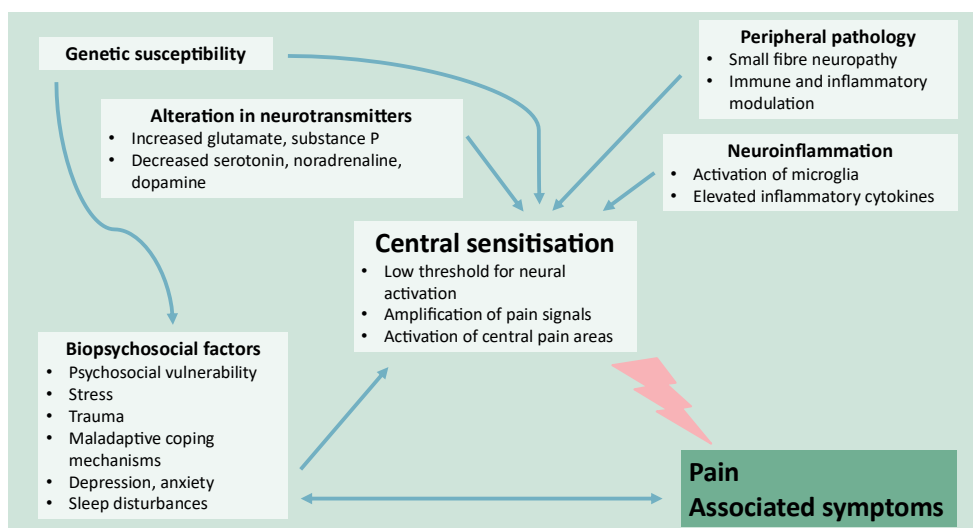


Figure 7: Schematic summary of the proposed mechanisms in the pathogenesis of fibromyalgia.

Treatment of FM

Due to the multifaceted nature of FM, a holistic approach to treatment is required. The treatment with the strongest evidence base is graded exercise, while psychological therapy for associated mood disorder and sleep difficulties is also recommended (115). Pharmacotherapy for depression and pain can be required but FM responds poorly to conventional analgesics (115,139-141).

Oral health and inflammation

Contact allergy in the oral cavity

Oral mucosal conditions are common and include stomatitis and oral lichenoid lesions (142,143). Stomatitis is a general term for painful inflammation of the oral mucous membranes, resulting in ulceration, swelling, and redness. It can be caused by infections, irritation, nutritional deficiencies or allergies (142). Oral lichenoid lesions most commonly present as lacy white striae on the buccal mucosa, but can also be erosive, atrophic, or hypertrophic (144). They can be associated with the systemic immune-mediated inflammatory condition lichen planus or can be caused by extrinsic factors such as contact reactions, where they are described as oral lichenoid reactions (OLR) (144).

The oral environment is exposed to a vast array of substances; foodstuffs, cosmetics, and dental materials, many of which are well-defined as contact allergens. However, considering this degree of exposure, clinical manifestation of contact allergy in the oral cavity is considered to be rare (145). The reasons for this remain unclear but the oral mucosa is generally more physically resistant to irritants and allergens than the epidermis, with salivary flow conferring additional physical protection (4,146). Conversely, the oral environment can be hostile to metals in particular, with saliva acting as an electrolyte in facilitating corrosion and release of ions. This can be further facilitated with alterations in salivary pH (147). Allergic contact stomatitis manifests as erythema, erosions, and hyperkeratosis, but clinical findings can be relatively scant in comparison with patient-reported symptoms which can include diffuse pain and burning.

Allergic contact stomatitis is considerably more prevalent in women, with dental metals being by far the most common contact allergens, followed by natural substances (including MP) and (meth)acrylates (145). Relevant sources of these allergens in allergic contact stomatitis and OLR are listed in the summaries of the specific allergens above. The association between allergy to carvone, a naturally occurring fragrance compound used in toothpastes and chewing gum, and OLR demonstrates the importance of careful assessment of the patient's own products and oral hygiene practices in evaluation of suspected contact allergy in the oral cavity (148-151). When associated with metal allergy, such as in dental restorations, OLR are usually localised to the site of contact with the metal, while those associated with fragrance and flavouring substances can be more widespread (149,152).

Relevant metal allergens in dentistry are listed in table 4. Note that metals are usually combined in alloys in dental restorations in order to optimise properties for the oral environment, including increased strength and improved corrosion resistance. Thus, assessment of suspected intraoral contact allergy to metals requires knowledge of the precise material used. Choice of dental material has changed over recent decades. With improved dental care and an ageing population, the use of fixed restorations has increased. Use of metals is declining with the availability of dental ceramic materials, composite resins, and glass ionomers, which are easier to use and have better aesthetic properties.

Table 4: Common dental metals in contact allergy.

Metal	Common alloys in dental restorations	Uses	Notes
Nickel	Chromium, titanium	Bridges, crowns, removable dentures	Case reports of sensitisation to dental nickel; may also induce immunological tolerance in non-sensitised individuals (145,153,154)
Palladium	Silver	Metal-ceramic crowns	Cross-reactivity and concomitant reactions with nickel (155-157)
Mercury	Amalgams with tin, silver, zinc, copper	Fillings	Banned in Sweden since 2009 and EU since 2025 due to environmental and health concerns (158)
Gold	Silver, copper, palladium, platinum, zinc	Inlays, bridges, crowns, posts	Discussed extensively in this thesis
Cobalt	Chromium	Bridges, crowns, removable dentures	Cobalt-chromium is the most common dental alloy used in Sweden (159)
Chromium	Nickel, cobalt	Bridges, crowns, removable dentures	

Periodontal disease

The periodontium is the tissues that surround and support the teeth. It consists of the gingiva (gums), the periodontal ligament, cementum (connective tissue), and alveolar bone. Periodontal disease can range from gingivitis — inflammation of the gums, to periodontitis — gingival recession, periodontal pockets, and alveolar bone destruction causing loosening and ultimately loss of teeth. It is caused by the development of plaque biofilm and subsequent bacterial infection of the gingiva leading to inflammation and ultimately destruction of the periodontium. Periodontal disease causes relatively few symptoms until in the severe stage; gingival inflammation and bone destruction are usually painless, but bleeding may be observed. Regular dental assessments are therefore paramount in the early identification of occult disease (160).

According to the World Health Organisation the estimated global prevalence of severe periodontal disease is 19% with a peak prevalence in late middle age (161). Due to heterogeneity in data collection and paucity of data from some regions, the true burden of periodontitis may be underestimated (162). Education in good oral care and habits are important, with poor oral hygiene and smoking being major risk factors for the development of periodontitis. Smoking cessation has been shown to improve the prognosis (163,164).

It is now established that periodontitis can be a driver in systemic inflammation, via transient bacteraemia and increased levels of systemic inflammatory mediators, and as such can be described as a multisystem disease (165,166). The prothrombotic

state of periodontitis is comparable with other systemic diseases (167). Periodontitis is strongly associated with cardiovascular disease and mortality (165). Diabetes both increases the risk of periodontitis and poor glycaemic control is related to degree of periodontal inflammation (168). Rheumatoid arthritis is also linked to periodontitis (169).

Periodontal disease is diagnosed clinically. Various classification systems are in current use but assessment of clinical attachment loss, ascertained with use of radiographs and probing periodontal pocket depth, is usually used to assess disease severity, while the grade (prognosis) is given by rate of deterioration and presence of modifying factors including smoking and diabetes (170-172). An illustration of periodontal disease and a simplified description of the staging and grading of periodontitis is shown in figure 8.

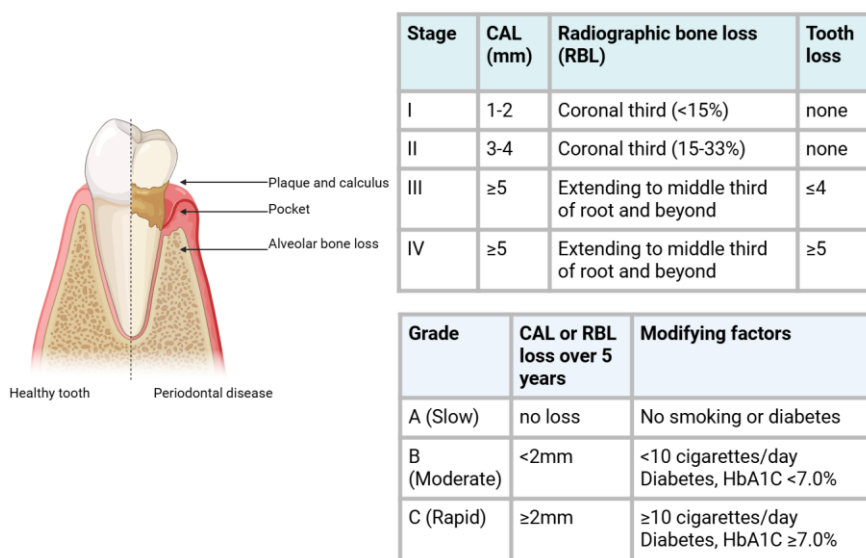


Figure 8: Illustration of periodontal disease and staging and grading of periodontal disease.

Adapted from the American Academy of Periodontology guidelines 2018 (173).

CAL, clinical attachment loss.

Knowledge gap and rationale

Since the identification of GSTS as a marker of gold allergy in the 1990s, the Department of Occupational and Environmental Dermatology (DOED) in Malmö has contributed extensively to the establishment of the clinical relevance of gold allergy in both localised reactions and systemic contact dermatitis. The timeline of key studies in gold allergy shown in figure 9 illustrates the progression of this work. Despite these advances, significant knowledge gaps remain. Whether contact allergy to gold in particular could manifest to the extent that it could cause pervading systemic symptoms such as seen in pain syndromes was not known. FM was chosen as a model for chronic pain.

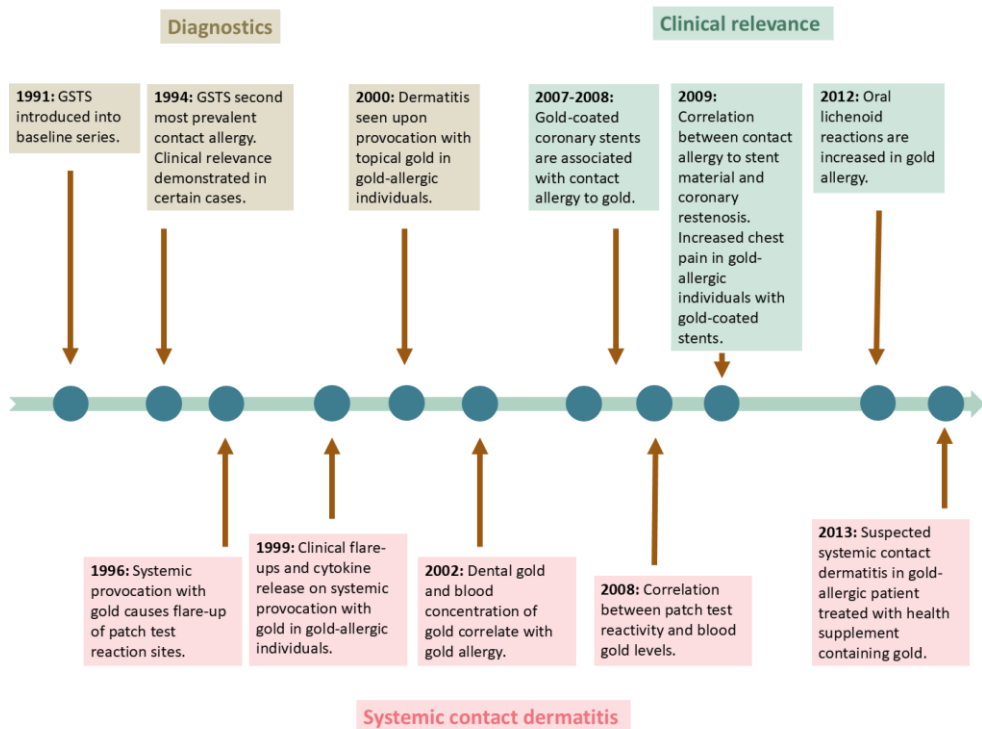


Figure 9: Summary of studies on gold allergy performed at the Department of Occupational Dermatology, Malmö (28,47,58,59,62,64-67,69,70,174-176).

The contact allergy profile of individuals with FM has not been systematically characterised. Although FM is frequently associated with self-reported environmental sensitivities, comprehensive investigations of contact allergy in this population are lacking. Multiple peripheral mechanisms have been proposed in the pathophysiology of FM but the potential contribution of contact allergy has not been explored. Investigation of this relationship would require prior characterisation of contact allergy within the FM population.

Preliminary findings on contact allergy in FM prompted a shift in focus of the project towards oral health. The observed allergy profile suggested that the oral environment may contribute to sensitisation and elicitation of contact allergy. Studies examining oral health in FM are limited, with existing research primarily addressing pain-related aspects, such as temporomandibular dysfunction. The project therefore aimed to investigate a potential multidirectional relationship between FM, oral health, and contact allergy.

Aims

The general aim of this project was to assess whether contact allergy could contribute to symptomatology in chronic pain syndromes, using fibromyalgia as a model. Given our knowledge of the role of gold allergy in systemic contact dermatitis, a specific focus on gold allergy would form part of the project. Our initial findings led to the second phase of the project, to explore whether oral status could be contributory to the contact allergy profile in individuals with fibromyalgia.

Specific aims

- To assess the prevalence and type of contact allergies in individuals with fibromyalgia and compare with control groups.
- To assess the clinical relevance of gold allergy in fibromyalgia.
- To examine the oral status of fibromyalgia patients and compare with controls.

Methods

Overview of studies included in the thesis

Phase 1 (Studies I-III)

Cross-sectional study of the prevalence of contact allergy in individuals with fibromyalgia in southern Sweden and comparison with control groups.

- a. Prior to patch testing, questionnaire distributed to the study participants including questions on past medical history, medications, known contact allergies and symptoms on exposure to allergens.
- b. Patch testing with the Swedish baseline series of contact allergens and an extended series of dental allergens.



Phase 2 (study IV)

Cross-sectional study of the oral status of individuals with fibromyalgia, both with and without gold allergy, and comparison with population controls.

Figure 10: Studies included in the thesis.

The author's contributions to each study were as follows:

Study I: Data analysis; participation in writing of manuscript.

Study II: Data analysis; writing of manuscript; submission process.

Study III: Data curation and analysis; writing of manuscript; submission process.

Study IV: Detailed planning of the study; planning and writing of the ethics application; construction of questionnaire; participant recruitment; attendance at study examinations; data curation and analysis; writing of manuscript; submission process.

Study Design and Participants

Studies I-III

Cross-sectional studies to assess the prevalence and type of contact allergy in FM, and the exposure and symptomatology to cutaneous and dental gold in individuals with FM.

FM Participants

Individuals with FM were recruited from the Swedish Fibromyalgia Association (*Fibromyalgiförbundet*) via information meetings at local branches in the regions of Skåne and Halland, southern Sweden, in the association journal, and written information sent to local branches. Individuals who expressed interest in participation were contacted by the research team and given verbal and written information on the proposed studies.

Controls

A summary of the different control groups used in studies I and II is outlined in table 5.

Table 5: Summary of the control groups used in studies I and II.

	Dermatitis controls	Population controls	Oral symptoms controls
Study I	Patients with suspected ACD tested at the DOED Malmö with the Swedish baseline series 2017-2018.	Participants drawn from a Malmö population study performed at the DOED Malmö 2011 (2).	—
Study II	Patients with suspected ACD tested at the DOED Malmö with Malmö extended baseline series 2018-2019.	—	Patients with oral symptoms tested at the DOED Malmö with the Malmö extended dental series 2019-2022.

ACD, Allergic contact dermatitis; DOED, Department of Occupational and Environmental Dermatology.

Study IV

A cross-sectional study performed to investigate aspects of oral health in individuals with FM via dental examination and a questionnaire, compared with general population controls.

FM participants

In 2021 all individuals who participated in studies I-III were contacted by telephone and in writing and offered participation in this study.

Controls

Age and sex matched controls were drawn from a cross-sectional dental epidemiological study performed in Jönköping, Sweden in 2013-14. This study was part of a longitudinal project with the aim of assessing the dental health of the general population. Randomly selected individuals in age bands of 10 years from 3-80 years were invited to participate in the study (total female participants 515).

Ethical approval and considerations

Ethical approval for studies I-III was obtained from the Regional Ethics Review Board, Lund, Sweden; dnr. 2017/487. Ethical approval for Study IV was obtained from the Swedish Ethical Review Authority (*Etikprövningsmyndigheten*); dnr. 2022-01573-01.

Written informed consent for all studies was obtained from participants. Control material for studies I and II was drawn from the database of patients held at the DOED in Malmö. Upon patch testing, approval is always sought from the individual for storage of patch testing details, and the patients are informed that data may be used for comparisons on a group level. Control material for study IV was obtained from register data where participants were informed that their data would be used at a group level for future studies.

Potential ethical concerns were considered and discussed prior to initiation of the studies. All investigations performed were standard investigations performed routinely in assessment of potential contact allergy and oral and dental health. Potential advantages to participants included improved knowledge regarding contact allergy and advice on allergen avoidance and potential treatment of any ACD. Similarly, the dental examination allowed a comprehensive analysis of oral health with any clinically identified problems being identified and further dental care being recommended.

Risks of participation were considered minimal. Commercial standard test preparations were used as far as possible to minimise any risk of active sensitisation from testing. Panorama radiographs were performed according to standard criteria, with minimal exposure to radiation.

It was judged that the potential individual and societal benefits of study participation, including an enhanced understanding of potential contributory factors in FM, would outweigh any risks of participating in the project.

Investigations

All investigations in the FM group took place in settings (meeting locales, hospitals, and dental clinics) located close to the participants' local FM patient association groups.

Patch testing

An overview of test protocols and patch test systems used is provided in table 6. A summary of test preparations is found in table 7. Occlusion time was 48 hours in all individuals. Patch test reactions were classified according to the guidelines of the International Contact Dermatitis Research Group and the European Contact Dermatitis Society criteria (9,12).

Communication between the FM participants and the dermatologists performing the readings was not permitted until the reading was completed to limit bias in test reaction interpretation. To facilitate interpretation of reactions to GSTS 2.0%, FM individuals with a 'doubtful reaction' to GSTS 2.0% at the first reading received additional testing with GSTS 5.0%. One reading of GSTS 5.0% was then performed in conjunction with the D7 reading. Participants were told to report late reactions that occurred after D7.

Table 6: Overview of patch test systems, preparations and routines used in studies I-III.

Study group		Patch test system	Amount of test substance applied	Patch test preparations ^a	Patch test readings
FM participants		IQ Ultra ^b	25 mg pet 20 µl aq	Swedish baseline series (2017) ^b Malmö extended dental series (2019) ^{b,e}	D3/4 and D7
Dermatitis controls	Study I	FC ^{b,c} FCA ^{b,c}	20 mg pet 15 µl aq	Swedish baseline series (2017)	D3/4 and D7
	Study II	FC FCA	20 mg pet 15 µl aq	Malmö extended baseline series (2018) ^{b,f}	D3/4 and D7
Oral symptoms controls (Study II)		FC FCA	20 mg pet 15 µl aq	Malmö extended dental series (2019)	D3/4 and D7
General population controls (Study I)		TRUE test ^d		TRUE test panels 1-3 (2011) ^d	D3/4
		FC ^b	20 mg pet 15 µl aq	Fragrance mix II ^g Sesquiterpene lactone mix ^g Components of fragrance mix I and II ^h	

Aq, liquid preparation; D, day; FC, Finn Chambers; FCA, Finn Chambers Aqua; Pet, petrolatum preparation; TRUE test, Thin-layer Rapid Use Epicutaneous Test.

^aSee table 7 for details of series and patch test preparations.

^bObtained from Chemotechnique Diagnostics, Vellinge, Sweden.

^cFC used in 2017 and FCA used from 2018 due to change in test system used at the DOED.

^dPreloaded patch test system. Obtained from SmartPractice, Phoenix, AZ, USA.

^eComplemented with GSTS 5.0% pet prepared at the DOED as required; see text.

^fSelected substances common to Malmö extended baseline series and Malmö extended dental series selected for analysis, see table 7.

^gFrom the Swedish baseline series.

^hSee table 2

Table 7: Summary of test preparations used in studies I-III.

Swedish baseline series (2017) (Concentration % and vehicle)	Dental series (2019) (Concentration % and vehicle)	TRUE test (2011) (Concentration mg/cm²)^a
Metals		
Cobalt chloride hexahydrate (1.0 pet)	Aluminium chloride hexahydrate (10.0 pet) ^b	Cobalt chloride hexahydrate (0.02)
Nickel sulphate hexahydrate (5.0 pet)	Ammonium hexachloroplatinate (0.1 aq)	Nickel sulphate hexahydrate (0.20)
Potassium dichromate (0.5 pet)	Calcium titanate (10.0 pet)	Potassium dichromate (0.023)
	Cobalt chloride hexahydrate (1.0 pet)	
	Copper sulphate (2.0 pet)	
	Elemental mercury (0.5 pet)	
	Elemental mercury (1.6 soft)	
	Elemental tin (50.0 pet)	
	Elemental titanium (50.0 pet)	
	Gold sodium thiosulphate (2.0 pet) ^b	
	Nickel sulphate hexahydrate (5.0 pet)	
	Potassium dichromate (0.5 pet)	
	Silver sulphate (10.0 pet)	
	Sodium tetrachloro palladate (3.0 pet) ^b	
	Titanium nitride (5.0 pet)	
Antimicrobials/preservatives		
Diazolidinyl urea (2.0 pet)	Formaldehyde (2.0 aq)	Diazolidinyl urea (0.55)
Formaldehyde (2.0 aq)	Glutaral (0.2 pet)	Formaldehyde (0.18)
Methylchloroisothiazolinone/ methylisothiazolinone (0.02 aq)	Sodium metabisulphite (1.0 pet)	Imidazolidinyl urea (0.60)
Methyldibromo glutaronitrile (0.5 pet)	Thimerosal (0.1 pet)	Methylchloroisothiazolinone/ methylisothiazolinone (0.0040)
Methylisothiazolinone (0.2 aq)		Paraben mix (1.0)
Paraben mix (16.0 pet)		Quaternium 15 (0.10)
Quaternium 15 (1.0 pet)		Thimerosal (0.008)
Natural substances		
Colophonium (20.0 pet)	Canada balsam (25.0 pet)	Colophonium (1.2)
Sesquiterpene lactone mix (0.1 pet)	Colophonium (20.0 pet)	
Plastics and glues		
Epoxy resin (1.0 pet)	1,4-Butanediol dimethacrylate (2.0 pet)	Epoxy resin (0.05)
p-tert-Butylphenol formaldehyde resin (1.0 pet)	1,6-Hexanediol diacrylate (0.1 pet)	p-tert-Butylphenol formaldehyde resin (0.045)

Phenol formaldehyde resin (1.0 pet)	2-Hydroxyethyl methacrylate (2.0 pet)	
	4-Tolyldiethanolamine (2.0 pet)	
	Benzophenone 3 (10.0 pet)	
	BIS-EMA (2.0 pet)	
	BIS-GMA (2.0 pet)	
	BIS-MA (2.0 pet)	
	Bornanedione (1.0 pet)	
	Dimethylaminoethyl methacrylate (0.2 pet)	
	Drometizole (1.0 pet)	
	Epoxy resin (1.0 pet)	
	Ethylene glycol dimethacrylate (2.0 pet)	
	Methylhydroquinone (1.0 pet)	
	Methyl methacrylate (2.0 pet)	
	N-ethyl-p-toluenesulphonamide (0.1 pet)	
	N,N-dimethyl-4-toluidine (5.0 pet)	
	Tetrahydrofurfuryl methacrylate (2.0 pet)	
	Triethylene glycol dimethacrylate (2.0 pet)	
	Urethane dimethacrylate (2.0 pet)	
Other topical agents		
Amerchol L-101 (50.0 pet) ^c		Wool alcohols (1.0) ^c
		Ethylenediamine Dihydrochloride (0.05)
Medications		
Budesonide (0.01 pet)		Budesonide (0.001)
Caine mix II (10.0 pet) ^d		Caine mix (0.63) ^d
Neomycin sulphate (20.0 pet)		Hydrocortisone-17-butyrate (0.02)
Quinoline mix (6.0 pet)		Neomycin sulphate (0.23)
Tixocortol-21-pivalate (0.1 pet)		Quinoline mix (0.19)
		Tixocortol-21-pivalate (0.33)
Colours and dyes		
p-Phenylene diamine (1.0 pet)		p-Phenylene diamine (0.09)
Textile dye mix (6.6 pet)		
Fragrances		
Fragrance mix I (8.0 pet)	Carvone (5.0 pet) ^b	Fragrance mix I (0.43)
Fragrance mix II (14.0 pet)	Cinnamal (1.0 pet) ^b	<i>Myroxylon pereirae</i> (0.8)
Lichen acid mix (0.3 pet)	Eugenol (2.0 pet) ^b	
<i>Myroxylon pereirae</i> (25.0 pet)	Hydroperoxides of limonene (1.0 pet) ^b	

	Hydroperoxides of linalool (0.3 pet) ^b	
	<i>Myroxylon pereirae</i> (25.0 pet)	
Rubber chemicals		
Black rubber mix (0.6 pet)		Black rubber mix (0.075)
Mercapto mix (2.0 pet)		Carba mix (0.25)
Thiuram mix (1.0 pet)		Mercaptobenzothiazole (0.075)
		Mercapto mix (0.075)
		Thiuram mix (0.025)

Aq, liquid preparation; BIS-EMA, 2,2-bis-(4-(2-methacryloxyethoxy)phenyl)propane, BIS-GMA, Bisphenol A glycerolate dimethacrylate; BIS-MA, Bisphenol A dimethacrylate; Pet, petrolatum preparation; soft, Softisan®; TRUE Test, Thin-layer Rapid use Epicutaneous Test.

^aTRUE test: Premanufactured patch test system; allergens incorporated into polyvinylpyrrolidone (povidone) gel matrix (vehicle).

^bSubstances common to Malmö extended baseline series and Malmö extended dental series selected for analysis in study II, dermatitis control patients.

^cAmerchol L-101 (Swedish baseline series): Lanolin alcohols. Wool alcohols (TRUE test): Cholesterol, lanosterol, agnosterol, straight- and branched-chain aliphatic alcohols (810 µg total).

^dCaine mix II (Swedish baseline series): Lidocaine (5.0% pet), Dibucaine hydrochloride (2.5% pet), Tetracaine hydrochloride (2.5% pet). Caine Mix (TRUE test): Benzocaine (378 µg), Tetracaine hydrochloride (66 µg), Dibucaine hydrochloride (66 µg).

Blood test for gold levels

Prior to patch testing, a blood sample was taken from the FM participants and analysed for blood gold levels. Detection limit for gold was set at 0.005 µg/L.

Questionnaires

Study I-III

FM participants filled in a questionnaire prior to patch testing. The questionnaire was divided into four sections as follows:

- Medical history including rheumatological, psychiatric, and dermatological conditions; medications and allergies; cutaneous and respiratory symptoms.
- Dental history, oral symptoms.
- Occupational exposures to nickel and gold; smoking status; piercings.
- Visual analogue scale (VAS) grading (0-100 mm) of FM severity in terms of pain, mood and fatigue over the previous week (177).

Study IV

Participants completed a questionnaire regarding aspects of oral health as follows:

- Oral hygiene habits.
- Experience of previous and current dental care.

- C. Dental materials and implants present.
- D. Oral symptoms and triggers for oral symptoms.
- E. Exposure and tolerance to different flavours and fragrances.
- F. The Oral Health Impact Profile (OHIP-14) questionnaire on oral health related quality of life (figure 11) (178,179).

The Oral Health Impact Profile (OHIP-14) questionnaire

A self-completed questionnaire consisting of 14 items subdivided into 7 domains. It measures social impacts of oral problems as a total score index. Scores for each question: 0 (never), 1 (hardly ever), 2 (occasionally) 3 (fairly often), 4 (very often). Maximum score 56.

Domain	Questions
1. Functional limitation	1. Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures? 2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?
2. Physical pain	1. Have you had painful aching in your mouth? 2. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?
3. Psychological discomfort	1. Have you been self-conscious because of problems with your teeth, mouth or dentures? 2. Have you felt tense because of problems with your teeth, mouth or dentures?
4. Physical disability	1. Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures? 2. Have you had to interrupt meals because of problems with your teeth, mouth or dentures?
5. Psychological disability	1. Have you found it difficult to relax because of problems with your teeth, mouth or dentures? 2. Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?
6. Social disability	1. Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures? 2. Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?
7. Handicap	1. Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures? 2. Have you been totally unable to function because of problems with your teeth, mouth or dentures?

Figure 11: The Oral Health Impact Profile-14 questionnaire (178,179).

Dental examination

Clinical examination was performed in the FM study group and the population controls with the following criteria recorded:

- Number of existing teeth.
- Dental caries.
- Presence of removable dentures.
- Number of surfaces with reconstructions: dental material was recorded and calculation of delayed and filled surfaces (DFS) was performed.
- Dental implants: presence and material.
- Oral mucosal findings.

- Gingival inflammation: defined as bleeding on gentle probing.
- Probing pocket depth.
- Radiographic examination: panoramic radiograph in all participants. In the control group, bite-wing radiographs were additionally performed in all participants, as well as a full-mouth periapical radiograph in individuals 60 years and older. Radiographs were used to confirm clinical findings of dental materials, determine whether gold posts were present, and to aid determination of stage of periodontal disease.
- Classification of periodontal disease according to clinical and radiological findings using the Hugoson and Jordan (H&J) criteria (1982) (171).

The examinations in the FM group were performed by two dentists calibrated as to the examination criteria. Examinations in the control group were performed by 11 dentists.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM, Armonk, NY, USA) versions 27-31. Where p -values were reported, a p -value < 0.05 was considered statistically significant.

Descriptive statistics were used to summarise the characteristics of the groups of participants and controls.

Categorical variables (for example, prevalence of contact allergy and categorical demographic data) were analysed with Pearson's chi-square or Fisher's exact test. Where appropriate, post-hoc analysis with the Bonferroni correction was applied.

Analysis of continuous data was performed with Student's t-test for independent variables, or the Mann-Whitney U-test where the data was not normally distributed. The Kruskal-Wallis test was used for comparison between multiple age groups. Negative binomial regression was used to control for age in count variable data. A general linear model was used to assess effect of variables on continuous outcome data.

Studies I and II

Controls were matched for sex and age with the FM group. The control group with oral symptoms was matched for sex alone due to the relatively low numbers of patients tested with this series at the DOED. Contact allergy rates for individual sensitisers were compared pair-wise between the FM group and the control groups. Comparisons with the dermatitis and the oral symptoms control groups were based on positive test reactions on one or both of the readings on D3/4 and day 7, while comparisons with the general population control group (baseline series) were based on the D3/4 reading. Additionally, a comparison between the FM and control groups

was conducted with respect to the number of individuals and the total number of positive reactions to grouped allergens.

For analysis of blood gold, all results including those below the detection limit of 0.005 µg/L were included.

Study III

Comparison of questionnaire responses according to allergy status (gold and nickel) was performed.

Study IV

For comparison with the population controls, the FM participants were banded into 10-year age groups from 30 to ≥ 80 years. From the control population, age-matched females were selected via a random number generator to achieve a ratio of 2:1 between control and FM participants in each 10-year age band. Regarding the different aspects of the dental examination, comparisons were made between the FM group and the population controls. Sub-analysis of responses to the OHIP-14 questionnaire and contact allergy within the FM group was also performed.

Results

Studies I and II

A total of 120 individuals with FM were recruited to the study. Only one of the participants was male and was excluded from subsequent analysis of results. Characteristics of the FM and control groups are illustrated in table 8.

Table 8: Summary of the characteristics of the study groups.
Age and sex matched

	FM participants	Study I		Study II	
		Dermatitis controls	General population controls	Oral symptoms controls	Dermatitis controls
Number	119	334	206	123	386
Mean age (SD)	59 (11.9)	59 (12)	58.5 (11.3)	61 (11.8) ^a	59 (11.9)

SD, standard deviation.

^agroup was not age matched

Patch test results

FM group

The prevalence of allergy to at least one substance was 44.5% in the Swedish baseline series, and 60.5% for the additional substances in the dental series. The most prevalent positive reactions are listed in table 9.

Table 9: The most prevalent contact allergens in the fibromyalgia group.
Total participants 119.

Substance	Prevalence n (%)
Nickel sulphate hexahydrate	31 (26.1)
Gold sodium thiosulphate (GSTS) 2.0%	30 (25.2)
-Including GSTS 5.0% and late reactors	40 (33.6)
Sodium tetrachloropalladate	24 (20.2)
<i>Myroxylon pereirae</i>	15 (12.6)
Fragrance mix I	12 (10.0)

N, number.

Swedish baseline series: FM and control groups

Comparison of the FM and dermatitis controls demonstrated significantly more reactions in the dermatitis controls for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) ($p = 0.0090$) and methylisothiazolinone ($p = 0.025$). The groups did not differ in total number of contact allergic reactions ($p = 0.32$).

Of the 25 allergens in the baseline series common to both the FM and population controls, there were significantly more reactions in the FM group for nickel ($p = 0.0004$), MP ($p = 0.00004$), and FM I ($p = 0.010$). There were significantly more reactions in total in the FM group ($p < 0.0001$).

Results of comparisons regarding positive reactions to at least one of the sensitisers and total number of contact allergies in groups consisting of metals, preservatives, fragrances, and rubber chemicals are demonstrated in table 10.

Table 10: Comparison between the fibromyalgia group and control groups regarding number of individuals reacting to grouped allergens and total number (n) of reactions to each allergen group.

For details regarding allergen groups see table 7. Comparisons with dermatitis controls based on day (D)3/D7 readings; comparisons with population controls based on D3 readings.

	Metals		Preservatives		Fragrances	
	≥ 1 allergy n (%)	Total n	≥ 1 allergy n (%)	Total n	≥ 1 allergy n (%)	Total n
Fibromyalgia group (n = 119)						
Day 3	27 (22.7)	32	6 (5) ^a 1 (0.8) ^b	7 ^a 2 ^b	21 (17.6)	32
Day 7	34 (28.6)	40	6 (5)	7	21 (17.6)	32
Dermatitis controls (n = 334)	95 (28.4)	114	30 (9.0) ^a	52 ^a	54 (16.2)	78
p-value			0.24	0.0096^c		
Population controls (n = 206)	25 (12.1)	32	5 (2.4) ^b	8 ^b	11 (5.3)	14
p-value	0.018	0.031			0.0007	< 0.0001

^a7 preservatives.

^b5 preservatives.

^cSignificantly more reactions in the dermatitis control group.

Dental series: FM and control groups

There was a significantly higher prevalence of reactions to GSTS 2.0% in the FM group when compared with the dermatitis controls (25.2% vs. 16.8%; $p = 0.043$).

Comparison of the FM group and the control group with oral symptoms demonstrated no difference in the total number of contact allergies ($p = 0.36$). Positive reactions to HEMA were significantly more prevalent in the FM group (5.0% vs. 0%; $p = 0.013$), while reactions to hydroperoxides of limonene were overrepresented in the oral symptoms control group (13% vs. 4.2%; $p = 0.021$). Analysis of grouped allergens demonstrated significantly more reactions in the FM group for (meth)acrylates and associated substances used in the manufacture of (meth)acrylates (table 11).

Table 11: Comparison between fibromyalgia and oral symptoms control group regarding total number (n) of reactions and number of individuals reacting to (meth)acrylates and associated substances.

For details regarding allergen groups see table 7.

	(Meth)acrylates	(Meth)acrylates and associated substances ^a	
	Total number of reactions n	Total number of reactions n	Individuals with ≥ 1 allergy n (%)
Fibromyalgia group (n = 119)	17	23	12 (10.1%)
Oral symptoms controls (n = 123)	3	4	3 (2.4%)
p-value	0.0012	0.00010	0.016

^aAssociated substances: 4-Tolyldiethanolamine, benzophenone 10, bornanediene, drometrizole, methylhydroquinone, N-ethyl-p-toluenesulphonamide, N,N-dimethyl-4-toluidine

Blood gold levels

Blood test for gold levels was performed in 117 of the FM participants. The mean blood gold level was 0.0056 $\mu\text{g/L}$. An outlier with blood gold level 0.269 $\mu\text{g/L}$ was found, this individual was taking colloidal gold as a health supplement. On exclusion of the outlier, the mean blood gold level of the remaining 116 FM participants was 0.0032 $\mu\text{g/L}$.

Study III

The questionnaire was completed by 118 of the FM participants, prior to patch testing. 25.4% of respondents reported cutaneous symptoms including itch and redness upon exposure to gold jewellery. Cutaneous symptoms upon contact with

non-precious metals were reported by 69.5% of respondents. Prevalence of oral symptoms including discomfort, redness or ulcers was 39.8%.

The number of patients with gold contact allergy (including GSTS 2.0%, GSTS 5.0%, late reactions, 40 in total) who reported cutaneous symptoms upon contact with gold was significant compared with those who did not have gold contact allergy (47.1% vs. 20.6%; $p = 0.010$). Gold contact allergy was also overrepresented in those with oral symptoms (58.3% vs. 34.7%; $p = 0.024$). There was no overrepresentation of gold contact allergy in self-reported presence of current or previous dental gold (28.9% vs. 32.4%; $p = 0.83$), and gold contact allergy was not overrepresented in those with a history of atopic eczema (41.9% vs. 36.4%; $p = 0.66$).

Nickel allergy was predictive of cutaneous symptoms upon exposure to non-precious metals. (90.6% vs. 71.6%; $p = 0.042$).

Analysis of VAS scores demonstrated that the FM individuals with oral symptoms scored higher on all domains (table 12). Those with gold allergy and oral symptoms had significantly higher VAS scores in all domains compared with those without oral symptoms (table 13).

Table 12: Visual analogue scale (VAS) analysis according to presence of oral symptoms.

VAS domain	Score (mean (SD))	Oral symptoms		
		Yes (mean (SD))	No (mean (SD))	<i>p</i> -value
Pain	61.78 (22.40)	64.79 (23.09)	58.26 (22.07)	0.081
General malaise	61.44 (22.39)	66.51 (21.71)	57.30 (22.59)	0.020
Tiredness	66.34 (21.02)	69.45 (22.57)	64.28 (19.58)	0.061

Table 13: Visual analogue scale (VAS) analysis according to oral symptoms in fibromyalgia individuals with gold allergy.

VAS domain	Gold allergy		
	Oral symptoms (mean (SD))	No oral symptoms (mean (SD))	<i>p</i> -value
Pain	69.86 (19.61)	55.8 (20.41)	< 0.001
General malaise	72.91 (15.73)	51.07 (20.81)	< 0.001
Tiredness	75.83 (18.21)	61.44 (19.93)	< 0.001

Study IV

A total of 60 individuals with FM were recruited to the study. Baseline characteristics of the participants did not differ from those who declined participation in this phase of the project (table 14). The age distribution of the FM participants is shown in figure 12.

The FM group and population control group did not differ in terms of current smoking status (6.7% vs. 9.4%; $p = 0.78$), educational attainment (university education 33.3% vs. 36.3%), or mean number of teeth (24.7 (SD 3.9) vs. 24.5 (SD 4.9); $p = 0.85$)

Table 14: Characteristics of fibromyalgia (FM) participants in study IV compared with FM non-participants.

Totals based on questionnaire responses in study I.

	Participants (n = 60) (%)	Non-participants (n = 59) (%)	p-value
Mean age	64.4 (SD 12.2)	62.6 (SD 11.6)	0.20
Smoking	6 (10)	3 (5)	0.31
Diabetes	1 (1.7)	2 (3.4)	0.62
Rash on exposure to fragrances	9 (15)	7 (11.9)	0.79
Rash on exposure to gold jewellery	17 (28.3)	13 (22.0)	0.39
Gold contact allergy	22 (36.7)	18 (30.5)	0.56
Oral symptoms	25 (41.7)	22 (49.2)	0.45

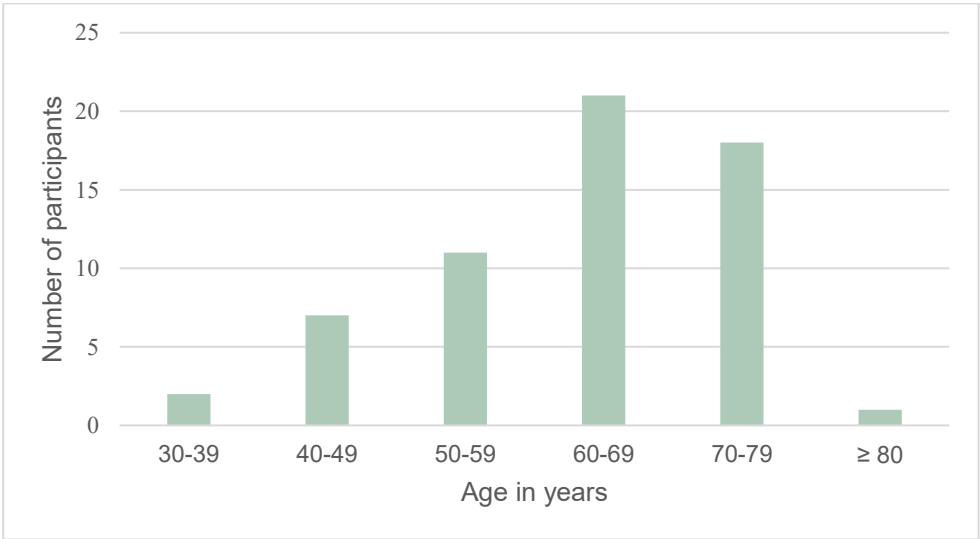


Figure 12: Age distribution of the fibromyalgia participants in study IV.

Oral care habits

All FM participants (60) and 118 of the control group answered the questionnaire on oral habits. All participants in both the FM and control groups responded that they brushed teeth daily with toothpaste. Other dental hygiene practices are summarised in table 15.

Table 15: Comparison of dental hygiene practices between fibromyalgia and population controls.

	FM group (n = 60) n (%)	Population controls (n = 118) n (%)	p-value
Daily use of dental floss or tape	44 (73.3)	34 (28.8)	< 0.001
<50 y	7 (70.0)	5 (29.4)	0.093
≥50 y	37 (74.0)	29 (28.7)	< 0.001
Daily use of interdental brushes	39 (65.0)	46 (39.0)	0.004

Oral symptoms

Oral symptoms were reported by 50% of participants in the FM group. Frequencies of different oral symptoms are shown in figure 13.

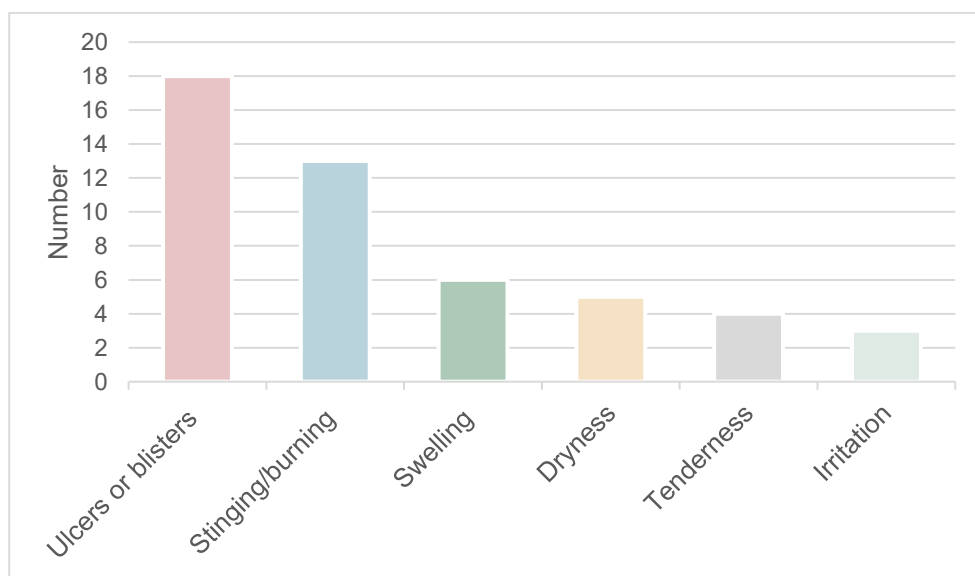


Figure 13: Prevalence of different oral symptoms in the fibromyalgia group.

Periodontal disease

The degree of periodontal disease differed significantly between the FM and control groups ($p = 0.017$), with post-hoc analysis demonstrating that moderate periodontal disease (H&J III) was significantly more common in FM (57.9% vs. 35.3%). In individuals < 50 years FM was associated with an increased severity of periodontal disease ($p < 0.001$).

Oral mucosal lesions

Mucosal lesions were more prevalent in the FM group (19 (31.7%) vs. 12 (10.08%); $p < 0.001$). A summary of the different mucosal findings in the FM group is presented in table 16. Lichenoid lesions were overrepresented in the FM group (11.7% vs. 4.3% ($p = 0.057$)).

Table 16: Prevalence of different oral lesions in the fibromyalgia group.

Lesion	Number of individuals (total = 60)
Lichenoid lesions	7
Irritation hyperplasia	5
Aphthae	2
Geographic tongue	1
Angular cheilitis	1
Coated tongue	1
Snus (tobacco) lesion	2

Oral Health Impact Profile (OHIP-14)

The mean OHIP-14 score in the FM group was 14.61 (SD 13.85). When banded into four age groups (30-49y, 50-59y, 60-69y, ≥ 70 y), the mean OHIP-14 score in the 30-49y group was 24.78 (SD 15.57) and in the ≥ 70 y group was 9.89 (SD 11.41). The total score between the age groups was significant ($p = 0.022$). Assessment of the different domains of the OHIP-14 showed statistically significant differences for functional limitation ($p = 0.030$), psychological discomfort ($p = 0.025$), physical disability ($p = 0.005$), and psychological disability ($p = 0.011$) when grouped for age, with a tendency to higher mean scores in the youngest age group.

Contact allergy

In the FM group, 73% had at least one contact allergy. Prevalence of allergy to substances in the Swedish baseline series was 41.7%. Gold was the most prevalent contact allergy (36.7%), followed by nickel (20%). No association between oral symptoms or mucosal lesions and contact allergy was found, and periodontal disease severity was not related to contact allergy.

Discussion

When this doctoral project was initiated, little was known about contact allergy in the fibromyalgia population. In the wider dermatological context, few studies have assessed potential associations between FM and cutaneous disorders. FM appears to be overrepresented in dermatological conditions including acne and psoriasis but cause and effect relationships are yet to be established, with the literature focusing on the high symptom burden in FM, in common with other co-morbidities in FM (180-182).

Patch testing a defined group of individuals (in this case with FM) can result in particular patterns of contact allergy where unifying explanations need to be sought to explain both prevalence and potential relevance. The contact allergies demonstrated in the contact allergy survey (studies I-III) led naturally to the study assessing oral health in the FM group (study IV). As with contact allergy, the oral health profile in FM has previously not been described in detail, which is somewhat surprising considering the reported high degree of oral symptoms in the FM group. The findings of study IV represent a step towards rectifying this discrepancy. The following discussion aims to contextualise the project findings in both the ACD and FM spheres.

Contact allergy in fibromyalgia

Studies I and II constitute the first published comprehensive survey of the prevalence of contact allergy in FM. Regarding the Swedish baseline series, rates of contact allergy in the FM group differed from the general population controls, with an increased total number of contact allergies in the FM group, and a contact allergy profile more resembling that of the dermatitis controls. One would expect that the FM group, with no known occupational or dermatological risk factors for contact allergy, would have a contact allergy burden akin to that of the general population rather than that of a group being investigated for contact allergy due to cutaneous symptoms (the dermatitis control group). There was also no difference in the total allergy rates in the dental series between the FM group and the oral symptoms control group ($p = 0.36$), where one may presume that the rates in the FM group would be lower. These findings lead naturally to two alternative and complementary explanatory hypotheses when considering contact allergy in FM: The *sensitisation*

hypothesis: that FM as a condition confers a higher probability for developing contact allergy via, as yet unidentified risk factor(s) and exposures; and the *elicitation hypothesis*: that specific contact allergies could be contributory factors in the development of FM. These hypotheses will be revisited throughout the discussion section, particularly in the following paragraphs on specific allergens.

Metals

Contact allergy to metals was overrepresented in the FM group, both regarding grouped metals when compared with the population controls, and to the specific metals nickel (when compared with population controls) and gold (compared with dermatitis controls).

That nickel was the most common contact allergen in the FM group is unsurprising; nickel remains the most prevalent contact allergy in testing with the European baseline series (19.8%) despite the introduction of the EU nickel restriction (88). This can be attributed to both allergies that developed prior to legislation and the fact that nickel is still widely found in jewellery items (183). Nickel allergy is considerably more common in women, due to higher exposure (184).

Gold was the second most prevalent contact allergen in the FM group (25.2%), becoming the most prevalent allergen if late reactions and reactions to GSTS 5.0% are included (33.6%). The prevalence of gold allergy may actually have been underestimated in the FM group due to the test system used; the IQ chambers detect fewer GSTS 2.0% allergies than the FCA used in the dermatitis and dental controls (185). Correcting for this would mean that the prevalence of GSTS 2.0% allergy would be 30.3% in the FM group, and significantly higher than both the dental and dermatitis control groups. Indeed, such high levels of gold allergy have previously been recorded in individuals with systemic exposure to gold via gold-coated coronary stents (66).

The high prevalence of palladium allergy in the FM group (20.2%) is likely to be due to cross-reactivity with nickel. The prevalence of palladium allergy in the FM group did not differ from control groups. Concomitant reactions between nickel and palladium are well described and isolated palladium allergy is rare (155). The main source of 'true' contact allergy to palladium is considered to be via palladium-containing dental implants which are rarely used in Sweden (155,186).

Metal hypersensitivity has long been of interest in chronic pain disorders. Studies have demonstrated that patients with subjective symptoms attributed to dental materials, including muscular pain and fatigue, had higher levels of metal allergies than controls, as well as a lack of concurrent localised oral symptoms (187). Additionally, high levels of nickel allergy were identified in patients with chronic fatigue syndrome (188). Further evidence for metals eliciting a systemic response (analogous to SCD) is provided by the systemic nickel allergy syndrome (SNAS),

where exposure to nickel in sensitised individuals via diet or dental and medical devices can lead to rheumatological, gastrointestinal, dermatological, and neurological symptoms (189). Benefits of treatment with low-nickel diets are uncertain (190).

As described in the introduction, accumulated evidence suggests that gold contact allergy can manifest as a SCD; aside from an elevation in inflammatory cytokines upon provocation with gold, gold-allergic individuals with gold-coated coronary stents have higher levels of coronary artery restenosis and angina than those without gold allergy (43,67-69). The main culprit source of systemic release of gold has historically been dental gold; dental gold is associated with gold contact allergy with a dose-response relationship, and gold levels in blood are correlated to amount of dental gold and gold allergy (59,62). However, dental gold has become less significant as gold has been superseded by alternatives. Indeed, only 5% of participants in study IV had objective evidence of dental gold on examination, although 20% described previous dental gold that had been removed due to oral symptoms or problems with the prostheses. In study III, 30% of respondents stated that they had current or previous dental gold, and assessment of the blood gold levels of the FM participants prior to patch testing demonstrated that those who reported dental gold had significantly higher blood gold levels than those without self-reported dental gold ($0.0056 \mu\text{g/L}$ vs. $0.0032 \mu\text{g/L}$; $p < 0.001$), in line with previous studies (Hopkins, unpublished data) (59,65). Previous studies have shown that approximately a third of individuals with dental gold have gold allergy, and that up to 74% of those with contact allergy to gold have dental gold (60,62,174). We can therefore conclude that the FM patients with gold allergy either have a high propensity to sensitisation to dental gold via the oral cavity, or that there may be additional factors to explain the high levels of gold allergy in this group, for example, percutaneously via gold jewellery.

Interestingly, in the pre-test questionnaire in study III, there was a significant correlation between symptoms upon exposure to gold jewellery and gold allergy in the FM group (i.e. clinical relevance of gold allergy) ($p = 0.010$), although the positive predictive value (PPV) of the question '*Do you experience, or have you previously experienced symptoms such as itching, redness, or swelling from direct skin contact with gold objects (e.g., jewellery)*' was relatively low at 32%. This can be partly explained by the generally high cutaneous symptomatology in the FM group; 25% experienced problems with gold jewellery and 69.5% had problems with contact with non-precious metals (nickel) (PPV for perceived nickel sensitivity and nickel allergy 35.4%). Pre-test questioning regarding other metal (nickel) sensitivity is known to have a low PPV (191). Clinical relevance of gold allergy regarding cutaneous exposure to gold has historically been considered to be doubtful at best. One study demonstrated an increase in dermatitis in patients with known gold allergy when provoked with gold in the form of gold earrings (58). Other studies have been unable to show relevance of gold allergy, either in the form of

pre-testing questionnaires or post-testing assessment of relevance (52,174). One can therefore hypothesise that the FM group have specific characteristics that contribute to the correlation between gold allergy and symptoms upon cutaneous gold exposure. Potential explanations are presented in the section 'explaining contact allergy in FM'.

Fragrances

The FM group had significantly higher levels of total fragrance allergy and specifically MP and FM I contact allergy when compared with the population controls. That reactions to different fragrance markers were seen is unsurprising; concomitant reactions to different fragrance markers are common (90). This can be due to cross-reactivity, presence of the same allergen in different test preparations of perfume markers, or independent sensitisation to multiple allergens (90). In the case of MP and FM I it is not uncommon to observe co-reactivity, due to the test preparations containing common substances including the emulsifier sorbitan sesquioleate (192,193). Testing both preparations is still recommended in routine investigation due to MP alone detecting relevant fragrance allergy in some cases (194).

The pattern of fragrance allergy in the FM group is of particular interest. When compared with population controls there was no overrepresentation of contact allergy to the other fragrance markers fragrance mix II, colophonium, or sesquiterpene lactone mix (195). The specific allergen limonene hydroperoxide was overrepresented in the oral symptoms control group when compared with the FM group. These findings would suggest that the FM individuals do not have a general sensitivity to fragrance but a more specific tendency to those substances that confer spice (cinnamon and clove) taste and aroma in foods, drinks, and dental products. Coupled with the overrepresentation of metal allergies as described above, this strengthens the hypothesis that oral exposure to allergens is of importance in FM.

'Food allergy' or intolerance is frequently cited as part of the spectrum of symptoms in FM, with sufferers frequently attributing deterioration in FM symptoms to foods or ingredients, and taking avoidant measures to prevent this (196,197). However, research has focused primarily on irritable bowel symptoms or immediate hypersensitivity reactions; contact dermatitis or SCD related to foods and spices has not previously been described in FM. Questionnaire responses in the FM group (Studies I-III) suggest that the FM individuals report high levels of subjective fragrance sensitivity when compared with dermatitis controls (Hopkins, unpublished data). Additionally, participants in study IV reported oral symptoms related to intake of food and drink (38.3%) or to toothpastes and mouthwashes (18.3%) (Hopkins, unpublished data). Further study is required to assess whether this has led to avoidant measures in the study group and whether the reported symptoms can be related to contact allergy or other mechanisms such as irritation

reactions. Such avoidant measures could also explain why certain flavouring/fragrance allergens were not overrepresented in the FM group (151).

(Meth)acrylates

Rates of allergy to grouped (meth)acrylates and to the specific allergen HEMA were significantly higher in the FM group than the control group of patients with oral symptoms. The prevalence of HEMA allergy at 5.0% is considerably higher than the 2-3% reported in female dermatitis patients in Europe (88,198).

Sources of sensitisation and clinical relevance of (meth)acrylate allergy can be difficult to unravel. Historically, clinically relevant manifestations of (meth)acrylate allergy were mainly seen with occupational exposures (including dental workers), and though (meth)acrylate allergy is often seen in patients with suspected allergic contact stomatitis, establishing clinical relevance can be difficult (11,145). One retrospective study estimated the relevance of HEMA allergy in patients with intra- and perioral complaints as 80%, but it is unclear as to how relevance was assessed (199). Currently, the most common source of non-occupational sensitisation to (meth)acrylates is via nail cosmetics (198).

A follow-up questionnaire was performed after studies I-III to attempt to ascertain potential sources of (meth)acrylate sensitisation in the FM group. Of 94 respondents, 57.4% had a history of use of (meth)acrylate-containing nail cosmetics. Eleven individuals had (meth)acrylate allergy and 91% of these had relevant exposure to nail cosmetics. Clinical relevance in the form of fingertip dermatitis was reported in 40% with (meth)acrylate allergy. No other occupational or recreational sources of (meth)acrylate exposure were reported (Hopkins, presented at the Congress of the European Society of Contact Dermatitis, Dresden, September 2024). In study IV, presence of composite dental material was seen in 59/60 participants. Prevalence of (meth)acrylate allergy was 10% with potential clinical relevance seen in 66.7% of those with (meth)acrylate allergy. Therefore, relevance of dental (meth)acrylate allergy in FM appears to be consistent with previous studies, and non-dental exposure to (meth)acrylates may have significance in FM. Again, the overall pattern of contact allergies in the FM group supports the hypothesis that the oral cavity can be of importance in sensitisation to contact allergens in FM.

Oral health and fibromyalgia

The dental study (study IV) was performed in response to the somewhat surprising results from studies I-III, and aimed to explore aspects of the ‘sensitisation hypothesis.’ The specific pattern of contact allergy observed suggests that oral

health may be of significance in FM; was there an increased exposure to these allergens in this group either via an increased allergen burden or specific characteristics of the oral environment and oral hygiene practices in FM?

Oral symptoms are commonly described in FM, with a prevalence of up to 70% (200). Difficulties can include xerostomia, glossodynia, and temporal mandibular joint dysfunction, with medications commonly used in FM including analgesics and antidepressants potentially contributing to the symptom profile (200-202). Despite this, there are a lack of studies reporting on objective oral findings in FM, with one study showing low prevalence of oral lesions despite a high symptom burden in participants (200).

Periodontal disease

FM was significantly associated with severity of periodontal disease, specifically in younger individuals (<50y). This suggests that FM may confer a risk factor in development of periodontal disease, with this factor becoming less significant with age as other risk factors and comorbidities (diabetes, cardiovascular disease) become more relevant. Oral hygiene practices do not appear to be contributory as a risk factor for periodontal disease in FM, with the FM group reporting more use of dental floss and interdental brushes than the population controls. Additionally, caries burden did not differ between the FM and control groups, again suggesting that oral hygiene does not play a decisive role in oral findings in FM. Whether FM individuals actually practice overly aggressive hygiene measures in order to mitigate perceived oral problems due to high symptom burden could potentially be contributory in development of periodontitis but this was not explored in the study.

The association between periodontal disease and systemic inflammation is well described, and may be a factor in FM, given that peripheral inflammation has been proposed as potentially contributory in the aetiology of FM (115,135,203,204). Periodontitis has also been shown to be associated with peripheral hyperalgesia, and a register study reported a bidirectional relationship between periodontal disease and FM (205,206). These findings suggest that the relationship between FM and periodontitis should be explored further in order to establish if periodontitis is a risk factor in the development of FM or vice versa, as has been seen in other systemic inflammatory disorders such as rheumatoid arthritis (169,207,208).

Oral lesions

The FM group had a significantly higher prevalence of oral mucosal lesions than the control group. Lichenoid lesions were overrepresented in the FM group, but this was not statistically significant (potentially due to small study group size). Presence of oral inflammatory lesions has been described in systemic inflammatory conditions but not in FM (209,210). Oral symptoms were reported in 50% of participants, of which ulcerations, blisters, and stinging/burning pain were the most common. There was a relative lack of objective findings given the high level of oral

symptoms in the FM group, consistent with previous study findings. This suggests that factors other than mucosal pathology contribute to oral symptoms in FM, in common with other symptomatology experienced in the condition. Previous authors have postulated that oral discomfort and temporomandibular disorders could be contributory in the process of central sensitisation in FM (211).

Quality of life in fibromyalgia

The high scores (14.27) recorded by the FM group in the oral health-related quality of life questionnaire employed in study IV (OHIP-14) indicating that the burden of oral symptoms has a significant negative effect in this group. Indeed, the mean score was considerably higher than that reported in the Swedish general population (4.3) and in individuals with severe periodontal disease (8.47) (179,212). Younger FM individuals had higher OHIP-14 scores, with the differences being most pronounced in the domains of functional disability and psychological disability. The relatively high burden of periodontal disease in the younger individuals may be contributory in this discrepancy, although periodontal disease severity was not associated with overall OHIP-14 scores in the FM group. It could be suggested that there is a two-way relationship between oral quality of life and FM, particularly in younger individuals, with general associated features of FM including poor general health status and psychosocial factors impacting oral quality of life symptoms, and oral symptoms influencing FM symptomatology.

Explaining contact allergy in fibromyalgia

The combined findings of studies I-III have revealed a specific contact allergy ‘profile’ in the FM study group, and the study focusing on a potential route to sensitisation and clinical elicitation of contact allergy — the oral cavity (study IV), has demonstrated interesting findings. Possible explanatory and unifying mechanisms for these observations are discussed in the following paragraphs.

Women

It is undisputed that contact allergy and ACD are more common in women than men, and FM is diagnosed predominantly in women (115,213-215). Concerning contact allergy, this difference is thought to be predominantly related to exposure patterns, and it can be said that the contact allergy profile in the FM study group reflects this, considering exposures to jewellery, perfumes and (meth)acrylates (nail systems). However, this does not explain why these allergies were elevated in the FM group in comparison with controls. FM is thought to be underdiagnosed in men

due to different patterns of presentation including more physical symptoms and less psychiatric comorbidity (215). Exploration of contact allergy in both men and women with FM may help to clarify the particular contact allergy profile in FM, and whether it is due to exposure alone.

Characteristics of the skin

Clinical-pathological characterisation of cutaneous disorders specifically in FM remains unexplored. Research suggests that skin conditions are common in FM, with prevalence of 43% described (182). A history of atopic dermatitis was reported by 31.6% of participants in study III. Atopy in FM has not been studied in detail but pain syndromes have been described as comorbidity in atopic disease (216). A link between inflammatory skin disease and the pro-inflammatory state seen in FM has been hypothesised, with peripheral inflammation amplifying and sustaining the nociceptive signals that contribute to central sensitisation, but this remains speculative (181,182). However, studies of skin biopsies in apparently clinically normal skin in FM individuals appear to support the ‘peripheral inflammation’ hypothesis, with overexpression of inflammatory cytokines, mastocytes, and N-methyl-D-aspartate (NMDA) receptors (which are involved in pain and itch regulation, as well as regulation of the epidermal milieu) (217-220).

Aside from environmental exposure, susceptibility to and elicitation of contact allergy is modulated by factors including the local cutaneous environment (friction, moisture, the skin barrier), while factors such as genetic susceptibility and psychological stress may also contribute to development of contact allergy, both generally and to specific allergens (4). The above immunohistopathological findings may therefore be relevant in both the sensitisation and elicitation hypotheses regarding FM and contact allergy. Further research aimed at characterising the skin profile in FM is therefore desirable.

The oral profile

Findings from Study IV would suggest that FM is characterised by a specific oral profile, with the high prevalence of oral symptoms including ulcerations and xerostomia accompanied by an increased burden of periodontal disease and lichenoid lesions.

No association was observed between oral symptoms, oral lesions, and contact allergy in the FM group. Possible explanations include the relatively low prevalence of dental metals in the FM group, with many participants stating that dental material had previously been removed due to oral symptoms or complications with the prostheses. These materials could therefore have previous significance in the oral symptom profile, with contact allergy and resultant symptoms potentially contributing to this. The overrepresentation of lichenoid lesions in the FM group should be explored further with particular reference to contact allergy, given that it is known that allergies to mercury, gold, and the flavouring/fragrance substance

carvone are overrepresented in oral lichenoid lesions (149,221). Specific analysis of dental hygiene products used by participants including toothpastes and mouthwashes was not performed in study IV, and is of potential importance given the fragrance/flavouring allergy profile of the FM group as outlined above.

Xerostomia was not directly measured in the study but could also confer another risk factor for the development of contact allergy given that salivary flow is thought to reduce exposure to oral allergens (145).

Whether periodontal disease could be linked to contact allergy in FM is an intriguing possibility. Limited study suggests that nickel-containing appliances can contribute to periodontal disease in allergic individuals, but there is no evidence to suggest that periodontitis increases susceptibility to contact allergy *per se* (222). The damaged periodontium could be considered to be analogous to a damaged skin barrier in increasing susceptibility to contact allergy, and oral lichenoid lesions, with a potentially atrophic and traumatised epithelium, could also enhance allergen penetration of the oral mucosa. A correlation has been seen between MP allergy and dental gold in patients with heart disease (coronary stents) with the authors suggesting that a poor oral (dental) status and increased dental interventions increase a general susceptibility to contact allergy (223).

Systemic inflammation

The schematic in figure 14 outlines proposed mechanisms between FM, contact allergy, and oral and systemic inflammation. The picture is far from complete, the dotted arrows representing potential routes for the elicitation hypothesis, i.e. that contact allergy, via a SCD, and periodontal disease can be contributory factors in the pathogenesis of FM. Box 1 describes a pilot study conceived to assess systemic inflammation in individuals with FM and gold allergy.

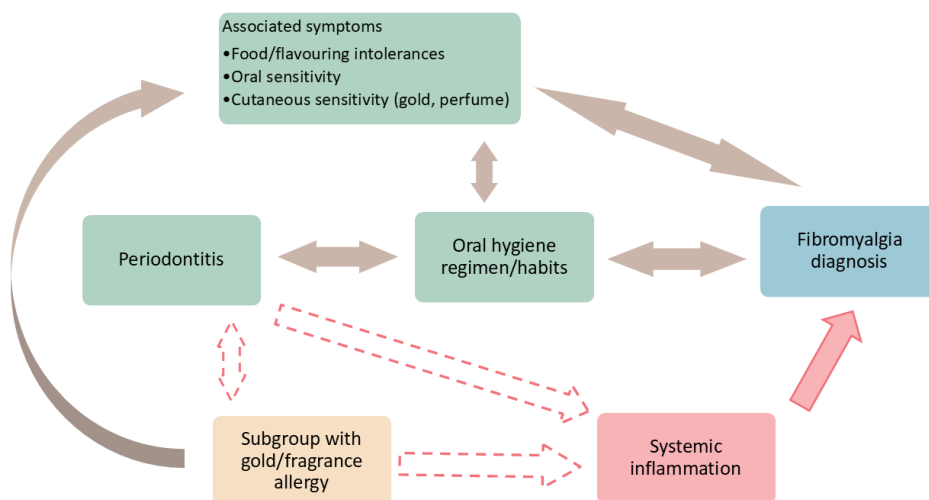


Figure 14: Proposed relationships between FM, contact allergy and periodontal disease.

Assessing systemic effects of gold exposure in individuals with gold allergy.

As part of the scope of the PhD project, a provocation study was conceived to assess the systemic effects of exposure to small amounts of gold over time.

FM individuals both with and without gold allergy would administer a daily dose of either a gold solution or placebo over an eight-week period. Measures of blood concentration of gold, blood cytokines, and aspects of severity of FM symptoms using a VAS scale would be made repeatedly over the course of the study.

Due to the onset of the COVID-19 pandemic, recruitment to the study was low and drop-out rates were high, rendering interpretation of results difficult due to small group sizes.

Increases in blood gold levels were seen in the participants who administered gold solution during the study period, demonstrating that ingestion of even small amounts of gold can have a measurable effect. Differences in cytokine levels and VAS scores were not observed between the individuals with or without gold allergy who administered gold solution. This can be attributed to the small sample sizes or gold levels not reaching a threshold to invoke a systemic response in gold-allergic individuals. However, the design of this pilot study serves as a model for future study into systemic effects of low-dose systemic exposure to allergens (Hopkins *et al.*, in manuscript).

Box 1: Provocation study assessing systemic effects of low-dose gold intake upon FM individuals with gold allergy.

Methodological considerations

Participant selection

The FM group were recruited via the local branches of the FM patient association (*Fibromyalgiförbundet*). This introduces potential recruitment bias; not all individuals with a diagnosis of FM will be members of said association. However, in the absence of a national register in Sweden of patients with FM this is perhaps the best way of reaching out to as many individuals with FM as possible. Patients with FM access healthcare through a variety of different sources including specialist clinics and primary care so recruitment via these centres would also risk exclusion of groups of individuals. Diagnosis of FM was not independently verified or reassessed for the purposes of the study, and criteria for diagnosis other than ‘physician diagnosed FM’ was not used. The patch testing process and dental examination required multiple visits, which would not be feasible for all patients. Potentially those who considered themselves to have sensitive skin or dental problems may have been more willing to participate. Where possible, visits were held as close as possible to the participants’ area of residence to facilitate attendance. The relatively small sample size of the FM individuals, and the skew towards older individuals limits the power of the analyses.

Control groups

The control groups for both the patch testing phase of the project and study IV were obtained using retrospective register data. Prevalence of contact allergy and aspects of oral health change over time, and one may therefore consider that the data are not directly comparable. All details about past medical history including FM diagnosis were not available. As FM is common in the general population it is likely that some individuals with FM were included in the control groups. In study II, the control group of dental patients was not matched for age due to low numbers of patients tested with this series. However, the mean age of the group did not differ considerably from the FM group. It would have been desirable to have an additional control group of individuals without a diagnosis of FM but tested for contact allergy in study IV.

Patch testing methodology

Different test systems were used in the FM and control groups. Some of the allergens used in the population controls also varied. It is known that different test systems differ in sensitivity in detection of contact allergy, but the correction method employed in estimating the prevalence of gold allergy in study II mitigates this to some extent (77,185,224). In study I, only one reading was performed at day 3 in the general population group, however, it is unlikely that fragrance allergy was missed as this is usually detected at the first patch test reading (225). It is known that patch test results are not always reproducible; they can vary in the same

individual over time and according to the investigator (226,227). Repeated patch testing was not performed in study IV for reasons of practicality.

Questionnaires

For all questionnaires, where possible, questions that had been employed and validated in previous studies were used. Standardised and validated scales of severity using both the VAS and OHIP-14 methods were used. The questionnaires were issued at the time of, and immediately prior to, the clinical examinations, meaning that the responses were not influenced by patch test or dental examination findings, and that the response rates were high. The use of paper questionnaires required manual data entry which carried the risk of incorrect entry of data. Details of participants' past medical and history were obtained via the questionnaires and responses were not calibrated with medical records meaning that comprehensive information regarding, for example, previous dental interventions could not be verified.

Importance

This project contributes to understanding of both contact allergy and oral health in FM, as well as the formulation of new hypotheses in the search for pathophysiological mechanisms in chronic pain syndromes. The project has been conducted in the real world setting and thus has direct implications for the individuals who participated in the studies. Potential beneficiaries include:

Individuals with FM

FM remains an enigmatic condition, with a high symptom burden. Contact allergy has not previously been studied in detail in FM, despite patients reporting both cutaneous and oral symptoms. Identifying relevant contact allergens (or exclusion of contact allergy) and providing treatment or prevention of ACD or oral manifestations of contact allergy is of importance in relieving one aspect of the patients' symptomatology, and one should have a low threshold for investigation of contact allergy if symptoms are suggestive of this.

Health and social economics

As FM represents a significant economic burden to the healthcare system, understanding and potentially alleviating contributory factors to the condition in the form of contact allergy would reduce both FM and dermatological costs, as well as improving efficiency of FM care. The potential improvement in work capacity for FM individuals would have positive societal consequences.

Oral healthcare providers

The discovery of the association between FM and periodontal disease, particularly in younger individuals with FM, is of significance for dental clinicians, with early intervention potentially reducing longer term morbidity. We recommend that dental providers are also alerted to the potential for inflammatory oral lesions in FM, and that poor oral quality of life is prevalent in FM, even in the absence of identified oral pathology. We suggest that assessment of impact of oral health upon quality of life forms part of the routine dental examination in FM so that appropriate interventions and measures can be signposted.

Contact allergy research

Uncovering new patterns of contact allergy is always of importance in the wider research field. The findings of this project can be applied to:

- i. Further research regarding routes to sensitisation within the oral cavity, and the relationship between intraoral pathology, contact allergy, and potential systemic effects of allergen absorption via the oral cavity and gastrointestinal tract.
- ii. Mapping contact allergy in specific conditions (FM) and patient groups, facilitating the stratification and efficiency of appropriate contact allergy investigation.
- iii. Contributing to the study of the extracutaneous manifestations of contact allergy, particularly regarding systemic inflammation and potential associations or similarities with other systemic inflammatory conditions.

Conclusions and paths for continued work

- **Individuals with FM have a specific pattern of contact allergy, with an overrepresentation of contact allergy to the metals gold and nickel, the fragrance and flavouring substances MP and FM I, and (meth)acrylates (Studies I and II).**

A potential route to sensitisation and elicitation of the above contact allergies is via the oral cavity. The above allergens are also associated with systemic contact allergy. Larger studies in different settings would assess whether these findings are generalisable to the FM population as a whole, or to other pain syndromes.

Detailed clinical examination, analysis of routes of exposure and correlation with contact allergy and symptoms is important both in identifying novel presentations of contact allergy and also potentially in the investigation of individuals with diffuse symptomatology.

- **Clinical relevance of gold allergy in FM has been demonstrated, with individuals with gold allergy experiencing cutaneous problems associated with the wearing of gold jewellery (Study III).**

Clinical relevance of the allergens identified in studies I and II should be explored further, including patterns of allergen exposure and characterisation of the local environment of the skin in FM. Could the cutaneous immunohistopathological findings previously described in the skin of FM individuals also be relevant in contact allergy or sensitivity to noxious stimuli?

- **Patients with FM have a poorer oral status than controls, particularly regarding oral mucosal lesions including lichenoid lesions, and burden of periodontal disease (Study IV).**

Periodontitis is a well-described route to systemic inflammation and is associated with systemic conditions. Larger, longitudinal studies would assist clarification as to the relationship between FM, periodontal disease, and oral mucosal inflammatory lesions. The association between oral symptoms, objective oral findings and FM should be clarified.

- **FM individuals with gold allergy report more oral problems than those without gold allergy. However, an association between oral symptoms, presence of dental material and contact allergies was not demonstrated in this project (Studies III and IV).**

The study sample was likely too small to assess whether contact allergy contributes to inflammatory status in FM and periodontal disease. Studies on larger populations with relevant dental and fragrance exposures are required to explore this further. Whether FM individuals practice avoidant behaviour to minimise allergen exposure should also be assessed.

- **Assessment of quality-of-life measures in FM shows that those with gold allergy score higher on the VAS domains of fatigue, malaise, and pain (Study III).**
- **Individuals with FM have high oral health impact scores, particularly in psychological and functional domains, with younger individuals particularly affected (Study IV).**

These findings serve to confirm the multifaceted impact of chronic disease. It is important for clinicians to adopt a holistic approach when assessing symptomatology and physical manifestations of illness.

- **Contact allergy may play a role in poorer oral status and systemic inflammation in fibromyalgia.**

The study of gold has provided a valuable model for understanding the complex interplay between material selection, environmental influences on material properties, and the resulting local and systemic immunological responses, particularly in the form of contact allergy. Although the use of gold in dentistry is declining, it continues to serve as an important reference for future research. Further investigations could involve both local and systemic provocation with relevant allergens to evaluate their impact on biological inflammatory parameters and associated symptoms. Additionally, studies involving larger populations are needed to better elucidate the potential relationship between contact allergy and both localised and systemic inflammation in chronic inflammatory conditions.

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